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VOLUME 47 OCTOBER 1943 NUMBER 4

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A CAUTION AGAINST TOO LIBERAL USE OF CITRATED BLOOD IN TRANSFUSIONS

JACQUES BRUNEAU, M.D.
AND
EVARTS A. GRAHAM, M.D.
ST. LOUIS

The use of citrated blood for transfusion has become so common in the last twenty-five years that it would seem to be entirely safe if ordinary precautions are taken to resort to compatible blood and to avoid the presence of pyrogens. Nevertheless, some experiences which we have had have caused us to question the innocuousness of sodium citrate itself, when injected in large quantity. The possibility of an overdosage of sodium citrate was especially suggested by the unexplained death of a patient who received 4,000 cc. of citrated blood in six hours after a revision thoracoplasty.

The toxicity of sodium citrate was well known when Lewisohn [1] introduced transfusion of citrated blood in 1915; its presence was blamed for the fact that the number of reactions associated with this method was greater than that associated with other methods (Unger,[2] Bernheim [3]). Drinker and Brittingham [4] and Unger [5] advanced some evidence showing that sodium citrate increased the fragility of the red blood cells, that it decreased the available quantity of complement and that it reduced the phagocytic power of the white blood cells and the function of the opsonins. However, these conclusions were not substantiated by the work of Mellon, Hastings and Casey [6] and Gichner.[7] Other factors have now been shown to be the cause of most transfusion reactions following the administration of citrated blood. The elimination of pyrogenic substances established by Seibert [8] and the improvements in the care of the apparatus stressed by Lewisohn and

From the Department of Surgery, Washington University School of Medicine and the Barnes Hospital.

1. Lewisohn, R.: A New and Greatly Simplified Method of Blood Transfusion, M. Rec. **87**:141, 1915.

2. Unger, L. J.: The Therapeutic Aspect of Blood Transfusion, J. A. M. A. **73**:815 (Sept. 13) 1919.

3. Bernheim, B. M.: Whole Blood Transfusion and Citrated Blood Transfusion, J. A. M. A. **77**:275 (July 23) 1921.

4. Drinker, C. K., and Brittingham, H. H.: The Cause of Reactions Following Transfusion of Citrated Blood, Arch. Int. Med. **23**:133 (Feb.) 1919.

5. Unger, L. G.: The Deleterious Effects of Sodium Citrate Employed in Blood Transfusions, J. A. M. A. **77**:2107 (Dec. 31) 1921.

6. Mellon, R. R.; Hastings, W. S., and Casey, G. H.: Observations on the Effect of Sodium Citrate on the Blood: Especially Considering the p_H Factor, J. A. M. A. **79**:1678 (Nov. 11) 1922.

7. Gichner, M. G.: Studies of Citrated Blood: Behavior of Platelets, J. A. M. A. **88**: 893 (March 19) 1927.

8. Seibert, F. B.: Fever-Producing Substances Found in Some Distilled Waters, Am. J. Physiol. **67**:90, 1923.

Rosenthal [9] have so reduced reactions following transfusions of citrated blood that their incidence is now no greater than when the blood is prepared by other methods (Lewisohn,[10] Zimmerman [11]).

From the very first, however, it was realized that too large amounts of sodium citrate could prove harmful. After experiments on dogs, Lewisohn [12] concluded that 15 Gm. would be a fatal dose for a man weighing 125 pounds (56.7 Kg.). He advised that 5 Gm. be the maximum dose used in transfusions. No mention was made, however, of the time over which such an amount could be given. Salant and Wise [13] in 1916 showed that for experimental animals the toxicity of sodium citrate depended on the rate of injection. This fact was demonstrated in human beings by Krautwald and Dorow.[14] They observed that tetany appeared in human subjects following the rapid introduction of 5 Gm. of sodium citrate intravenously (i. e., in a few minutes) and that the rapidity of onset and the severity of symptoms varied with the dose and the rate of administration.

Since Lewisohn's pioneering work in 1915, the dosage limit set by him often has been exceeded. Marriott and Kekwick [15] reported giving as much as 5,600 cc. of citrated blood over a period of forty-eight hours. It is to be noted that all the reported massive transfusions were given slowly, i. e., over a relatively long period. In recent years, however, broadening of the indications and scope of major surgical procedures and better understanding of the advantages of transfusions in cases of shock and hemorrhage have led to a more frequent and quantitatively greater use of blood as well as to its more rapid injection. This work was undertaken in an effort to determine the effects of the introduction of large quantities of citrated blood in a short period.

EXPERIMENTAL PROCEDURE

The experimental procedure consisted of bleeding unanesthetized dogs 1 per cent of their body weight at half-hourly intervals. The blood obtained, after being mixed with an anticoagulant, was reinjected intravenously. Mongrel dogs were used, and with a few exceptions they were kept only a few days before being submitted to the experimental procedure. All were made to fast for eighteen hours previous to the experiment. The bleeding was carried out through a cannula introduced into the femoral artery. The blood was injected by means of an ordinary transfusion set into the femoral vein on the opposite side. The rate of flow was regulated so that the transfusion was almost completed in thirty minutes. Blood pressure readings were obtained with a mercury manometer before each bleeding. At regular intervals, samples of venous blood were obtained from the site of injection for determination of hematocrit values, clotting time and calcium and phosphorus content. This procedure was carried out on two groups of dogs. In group A (8 dogs) sodium citrate was used as an anticoagulant. Enough of a 5 per cent solution was mixed with the blood to obtain a final concentration of 0.6 per cent sodium citrate. In group B (8 dogs) heparin [16] was used as a control, 0.085 cc. of heparin diluted in 5 cc. of saline solution being added to each 100 cc. of blood. Between 10 and 20 cc. of blood was lost through different causes at each bleeding.

9. Lewisohn, R., and Rosenthal, N.: Prevention of Chills Following Transfusion of Citrated Blood, J. A. M. A. **100**:466 (Feb. 18) 1933.

10. Lewisohn, R.: Twenty Years' Experience with the Citrated Method of Blood Transfusion, Ann. Surg. **105**:602, 1937.

11. Zimmerman, L. M.; Strauss, A. M., and Laufman, H.: Blood Transfusion Reactions: Their Causes and Prevention, Ann. Surg. **114**:961, 1941.

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13. Salant, W., and Wise, L. E.: The Action of Sodium Citrate and Its Decomposition in the Body, J. Biol. Chem. **28**:27, 1916.

14. Krautwald, A., and Dorow, H.: Ueber die Verträglichkeit grösserer intravenöser Natriumcitratgaben, Arch. f. exper. Path. u. Pharmakol. **194**:691, 1940.

15. Marriott, H. L., and Kekwick, A.: Continuous Drip Blood Transfusion, Lancet **1**:977, 1935.

16. From the Lederle Laboratories, Inc., Pearl River, N. Y.

EXPERIMENTAL RESULTS

For dogs in group A, in which replacement was effected with citrated blood, the average survival period was slightly over four and one-half hours (chart 1). These animals withstood an average of nine and twenty-five hundredths bleedings before death. In 5 of these dogs, dyspnea, convulsions or fibrillary twitchings were observed prior to death. In 3 dogs dyspnea alone was noted. Individual variations were not outstanding in this group of animals. For group B the average survival period was almost three times as long, i. e., over twelve

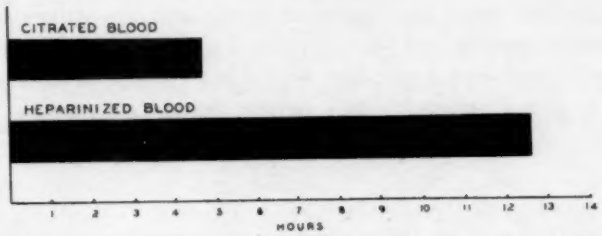

Chart 1.—Survival of dogs receiving heparinized blood and those receiving citrated blood.

TABLE 1.—*Serum Calcium Values for Four of the Dogs Given Transfusions of Citrated Blood*

Number of Dog	Serum Calcium, Mg. per 100 Cc.	
	Initial (Before Experiment)	Terminal (Before Death)
12	10.7	16.5
15	12.6	15.4
19	8.5	10.5
30	10.0	13.3

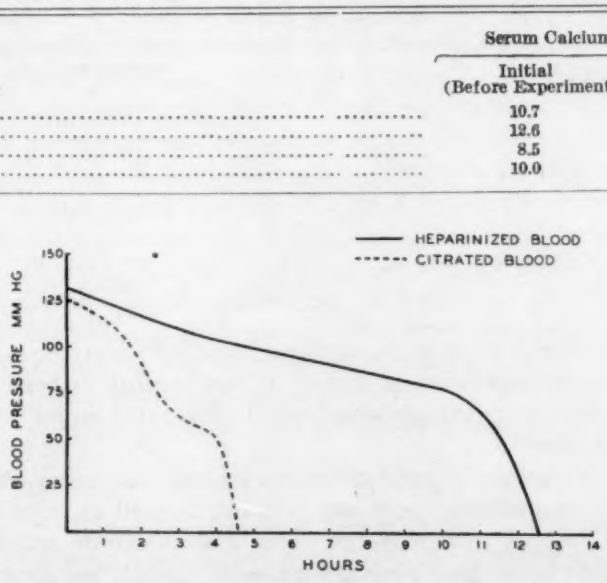

Chart 2.—Average blood pressure curves observed in the animals given transfusions of heparinized blood and those given transfusions of citrated blood.

and one-half hours, corresponding to an average of 25.2 bleedings (table 1). In no instance were convulsions and fibrillary twitchings noted. The individual variations in this group were greater than in group A.

In group A the blood pressure was observed to drop to a relatively low level even two and one-half hours before death. No similar drop was noted in the animals receiving heparinized blood (group B) (chart 2).

In both groups the hematocrit values were comparable and changed little during the course of the experiment. The average drop in the reading was 4 points. One animal in each group, however, had a rise of 5 points.

In group A, during the first hour, the clotting time, as determined by the Howell method, showed a slight but constant decrease, averaging two and eight-tenths minutes. Shortly before the death of 3 dogs in this group the clotting time had increased by about ten minutes, but the other 5 animals showed no significant changes. In group B, the clotting time did not show any initial decline and in all animals it was greatly lengthened toward the end of the experiment, the maximum increase being seventy-two minutes.

The serum calcium values determined for 4 dogs given transfusions of citrated blood showed a definite increase prior to death (table 1). There were no significant changes in the initial and terminal serum calcium values of 7 of the dogs given transfusions of heparinized blood (table 2). Unfortunately, reliable determinations of serum phosphorus could not be made in many instances, because some specimens had to stand several hours before being analyzed.

COMMENT

The animals given transfusions of heparinized blood survived, on the average, almost three times as long as those given transfusions of citrated blood. Moreover, the latter showed before death definite toxic symptoms not seen in the

TABLE 2.—*Serum Calcium Values for Seven of the Dogs Given Transfusions of Heparinized Blood*

Number of Dog	Serum Calcium, Mg. per 100 Cc.	
	Initial (Before Experiment)	Terminal (Before Death)
29	10.5	9.9
13	10.9	10.5
14	8.3	8.4
28	10.0	10.3
35	10.4	9.7
36	*10.3	10.9
38	12.2	11.8

former. These differences indicate that citrated blood given in very large amounts over a short period is inferior as a means of replacement to heparinized blood and may even be harmful, owing undoubtedly to the rapid introduction of large amounts of sodium citrate.

A comparison of the blood pressure curves for the two groups suggests that citrated blood will not maintain the blood pressure as well as heparinized blood. This may possibly be due to a toxic effect of sodium citrate manifesting itself even two hours before lethal conditions are attained. Love [17] has shown previously that injection of 35 mg. of sodium citrate per kilogram of body weight depresses the action of the heart muscle. In view of the wide variation present in biologic experiments of this kind, we feel that the evidence is not sufficiently strong to be more than suggestive of this conclusion.

The paradoxic shortening of the clotting time observed early after the administration of citrated blood corroborates the findings of Lewisohn.[1] This effect was at one time advocated by Neuhof and Hirschfeld [18] as a therapeutic measure for internal hemorrhage. This phenomenon has been attributed to injuries

17. Love, G. R.: Studies on the Pharmacology of Sodium Citrate: I. Circulation, J. Lab. & Clin. Med. **9**:175, 1923.

18. Neuhof, H., and Hirschfeld, S.: Slow Intravenous Administration of Large Doses of Sodium Citrate: New Method of Control of Bleeding, New York M. J. **113**:95, 1921.

to the platelets, but no satisfactory explanation exists at this time. On the other hand, the lengthening of the clotting time observed after massive transfusions with heparinized blood was so great as to militate against the use of this method in other than small routine transfusions. This was true even though the amount of heparin used in the present experiments was too small to prevent clotting entirely. A large needle had to be used, and even this would not prevent the flow of blood from being slowed or even stopped by clotting. This is in accordance with the previous observations reported by Sappington.[19]

Sodium citrate forms with calcium a complex soluble salt which liberates very few calcium ions. The characteristics of this substance have been established by a study of its chemical behavior (Sabbatani [20]), by conductivity measurements (Shear and Kramer [21]) and by its pharmacologic action (Hastings and McLean [22]). It is generally held that it is the formation of this salt which prevents the clotting of blood in vitro by removing the calcium ions necessary for coagulation. The tetany observed in animals and man following the intravenous administration of sodium citrate is attributed to the same phenomenon. Death also probably can result from this cause. Whether the death of our animals was due to this action of sodium citrate must remain unanswered until a more practical method of determining the ionized calcium in the blood becomes available.

Actually, there is a great variation in the reported effects of sodium citrate on the total calcium content of the blood. Tsai and Hsu [23] showed that its intravenous injection resulted in a slightly decreased plasma calcium which reverted to normal in twenty-four hours. By the slow intravenous injection of a 1.5 per cent solution of sodium citrate, we were able to confirm these results in contrast to the increase in total calcium observed in our experiments in which repeated transfusions of citrated blood were given. Shohl [24] and Krautwald and Dorow [14] have stated that the total calcium level does not change as a result of administration of citrate. Hastings [25] seems to have agreed with the authors just mentioned; in addition, he showed that if excretion and oxidation are prevented by tying off the kidneys and liver calcium is drawn from the body stores and the total calcium of the blood is increased. Using the microincineration technic, Scott and Lansing [26] have demonstrated that administering sodium citrate to cats by perfusion will lead to depletion of the body cells in calcium and magnesium. At present, however, it

19. Sappington, S. W.: The Use of Heparin in Blood Transfusion, J. A. M. A. **113**:22 (July 1) 1939.

20. Sabbatani, L.: Calcium et citrate trisodique, Arch. ital. de biol. **36**:397, 1901.

21. Shear, M. J., and Kramer, B.: Composition of Bone: Some Properties of Calcium Citrate, J. Biol. Chem. **79**:161, 1928.

22. Hastings, A. B.; McLean, F. C.; Eichelberger, L.; Hall, J. L., and Da Costa, E.: The Ionization of Calcium, Magnesium and Strontium Citrates, J. Biol. Chem. **107**:351, 1934.

23. Tsai, C., and Hsu, F. Y.: Effect of the Intravenous Injection of Sodium Citrate and Oxalate on the Concentration of Plasma Calcium and Inorganic Phosphorus, Chinese J. Physiol. **4**:273, 1930.

24. Shohl, A. T.: Mineral Metabolism, New York, Reinhold Publishing Corporation, 1939, p. 137.

25. Hastings, A. B., cited by Shohl.[24]

26. Lansing, A. I., and Scott, G. H.: The Effects of Perfusion with Sodium Citrate on the Content and Distribution of the Minerals of Various Cells of the Cat as Shown by Electron Microscopy and Microincineration, Anat. Rec. **84**:91, 1942.

is only on hypothetic and questionable grounds that one would suggest that the increases in total serum calcium observed in the present experiments are due to a withdrawal of calcium from the tissues and are an expression of an alteration of the degree of calcium ionization in the circulating blood.

The presence of sodium citrate appears to be responsible for the earlier death of the dogs in group A, but it may not be the only factor. For example, we have given other dogs equivalent amounts of sodium citrate over a similar period of time. None of these experiments resulted fatally. This would seem to indicate that a lethal amount of sodium citrate was not attained in the experiments which have been reported. The ultimate death of the dogs given transfusions of heparinized blood shows that the repeated insults inflicted on the organism during our experiments produce in themselves deleterious effects. Whether these conditions will lead to decreased tolerance to sodium citrate is not known. But the findings of Hastings would indicate that the lowering of the blood pressure observed in these experiments might decrease the tolerance of the organism by rendering renal elimination and hepatic oxidation less effective.

However, under these experimental conditions it seems that the earlier deaths of the animals in group A should be ascribed to the presence and effects of excessive amounts of sodium citrate, although very little light can be thrown on the mechanism of this action.

The clinical application of these experimental findings is difficult. There is no evidence at hand as to the exact rate of oxidation and elimination of sodium citrate in human beings. Since its toxic effects have been shown to vary with the dosage and repetition of a certain dose, with the rate of administration, with different animal species and even with individual members of the species, the safe amount to be injected under given conditions cannot easily be determined. To duplicate our experimental conditions, a man weighing 70 Kg. would have to be given 6,300 cc. of blood containing 0.6 per cent citrate within a few hours. The concentration of 0.6 per cent used in these experiments is higher than that in general use. Since the advent of blood banks, however, concentrations often have been increased up to 0.5 per cent and even higher. Patients requiring the rapid administration of such large amounts of blood are usually desperately ill. Whether their condition decreases their tolerance to sodium citrate is not yet known. All these factors make it impossible to establish the safe amount of citrated blood to be given in a certain period. Quantities of 2,000 or even 3,000 cc. in a few hours have been given without apparent ill effects. From our experimental evidence we feel that a warning should be given against the too liberal use of citrated blood. When extreme conditions prevail and such amounts have been given within a few hours, it would seem advisable to resort to other methods if blood must still be given.

SUMMARY

Dogs bled repeatedly and continually given transfusions of citrated blood survived a much shorter time than controls receiving heparinized blood.

This difference seems to be due to the toxic action of large amounts of sodium citrate. The possible mechanism of its action is discussed on purely theoretic grounds.

The clinical implication of these findings is a warning against the too liberal use of large amounts of citrated blood over a very short time.[27]

Barnes Hospital.
600 South Kingshighway Boulevard.

27. After this work was practically completed, we saw the important article of A. C. Ivy, H. Greengard, I. F. Stein, F. S. Grodins and D. F. Dutton (The Effects of Various Blood Substitutes in Resuscitation After an Otherwise Fatal Hemorrhage, Surg., Gynec. & Obst. **76**:85, 1943). Their results with citrated plasma and citrated blood were definitely inferior to those obtained with heparinized plasma, as determined by survival rates in experimental animals following a single massive hemorrhage. It is noteworthy that our experiments, performed in a somewhat different manner, likewise demonstrated the undesirability of large amounts of citrated blood.

EFFECTS OF MORPHINE IN EXPERIMENTAL SHOCK DUE TO HEMORRHAGE

ALFRED BLALOCK, M.D.
BALTIMORE

The following statements regarding the use of morphine in the treatment of injured patients were made by Cannon [1] in 1923:

> Concerning the use of morphine there have been differences of opinion. It has been given to badly wounded men hypodermically even in as large a dose as one grain [0.06 Gm.]. Crile and Lower have advocated giving the drug to the point at which respiration sinks to at least 12 per minute. On the other hand Marshall, who has had very large experience in anesthetizing shocked men, has testified that the severely wounded, when deeply morphinized, make an unsatisfactory recovery after operation. . . . As experiments have proved, after morphine the blood pressure may be lowered further without producing acidosis than is possible otherwise, an observation which suggests that morphine lessens metabolism at a time when the oxygen, needed for the maintenance of chemical changes in the cells, is likely to be insufficient. The drug should be given therefore until the patient is comfortable and quiet. In some cases ¼ grain [0.015 Gm.] may be sufficient, in others ½ grain [0.03 Gm.] may be needed. The dose should be repeated if necessary.

It is generally agreed at the present time that the use of morphine is indicated in the treatment of the majority of patients with severe injuries, exceptions including those with intracranial damage. There is, however, a difference of opinion as to the dose. Some are of the opinion that the routine dose for an injured adult should be ½ grain (0.03 Gm.) hypodermically, whereas others maintain that this amount is dangerous and that a single injection should not exceed ¼ grain (0.015 Gm.), to be repeated if necessary. Dogmatism regarding the dosage appears to be necessary because the nature of present warfare is such that a physician is not always at hand, and the drug in proper form and dose should be available for administration by the injured person or by an associate.

Large doses of morphine usually cause nausea and vomiting and often diarrhea when administered to dogs. Such effects are observed less frequently in man, but they do occur. Since with dogs large amounts of morphine cause the loss of fluid from the body in the vomitus and stools, the question arises as to whether the drug decreases tolerance to bleeding. Hemorrhage was chosen as the method for causing peripheral circulatory failure, because it is probably the most common cause of shock in injured human beings and because the effects can be studied experimentally without the necessity for producing deep narcosis.

METHODS AND RESULTS

Large animals were used in all experiments. They were given no food but were allowed water during the eighteen hours preceding the determination of the blood volume. The dye-dilution method (T-1824) as revised by Price and Longmire [2] was used for determinations of plasma volume, and the blood volume was calculated after the hematocrit reading had been

From the Department of Surgery of the Johns Hopkins University and Hospital. The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Johns Hopkins University.

1. Cannon, W. B.: Traumatic Shock, New York, D. Appleton and Company, 1923.

2. Price, P. B., and Longmire, W. P.: The Use of T-1824 in Plasma Volume Determinations, Bull. Johns Hopkins Hosp. **71**:51, 1942.

determined on arterial blood by the use of Wintrobe tubes. The experiment proper was performed twenty-four hours after the studies on blood volume. A total of 20 experiments was performed. Ten of the animals were given hypodermically 1 mg. of morphine sulfate per kilogram of body weight. All of these animals vomited, and 3 of the 10 had loose bowel movements. The morphine was given thirty minutes before the beginning of the experiment. No anesthetic agent was used for the remaining 10 animals except for the injection of procaine hydrochloride at the site at which a cannula was placed in the femoral artery.

The removal of blood from the femoral artery was carried out as follows: At the beginning of the experiment, blood equal to 10 per cent of the calculated blood volume was withdrawn and the animal was removed from the table. This procedure was repeated one hour and two hours subsequently. Thereafter, blood equal to 2.5 per cent of the original blood volume was removed at fifteen minute intervals until death ensued. The experiments were performed in pairs, one animal having had morphine and the other not having had it, and an attempt was made to use dogs of essentially the same weight and build.

The Effects of Morphine on the Bleeding Volume

Narcotic	Experiment No.	Body Weight, Kg.	Plasma Volume, Cc.	Hematocrit Reading	Whole Blood Volume, Cc.	Total Quantity of Blood Removed		Hematocrit Reading	
						Per Cent Blood Volume	Per Cent Body Weight	Control	Terminal
Morphine sulfate	1	13.7	690	49.8	1,300	61.2	5.8	43.7	30.0
	3	13.1	609	55.2	1,333	47.5	4.8	50.4	43.5
	5	12.5	841	43.5	1,478	60.0	7.1	42.0	22.3
	7	11.4	699	52.0	1,458	57.5	7.3	49.4	39.6
	9	15.8	749	55.1	1,652	50.0	5.2	55.4	56.2
	11	12.8	700	50.6	1,460	50.0	5.7	49.6	52.2
	13	11.5	701	38.0	1,129	52.5	5.3	43.3	36.8
	15	9.7	462	51.2	877	57.5	5.2	45.0	37.2
	17	11.0	588	35.0	842	47.5	3.6	36.5	35.3
	19	11.7	517	49.8	1,036	45.0	4.0	46.7	40.4
None	2	14.0	536	52.1	1,120	60.0	4.8	49.0	35.4
	4	12.2	755	47.1	1,378	45.0	5.1	46.8	42.2
	6	12.4	743	47.0	1,390	65.0	7.3	43.2	28.4
	8	11.8	645	50.0	1,255	47.5	5.1	51.3	47.3
	10	15.0	712	48.8	1,400	45.0	4.2	44.4	44.7
	12	14.4	890	38.8	1,460	47.5	4.7	38.6	31.4
	14	12.5	792	48.5	1,540	50.0	6.1	50.0	48.3
	16	8.4	622	33.4	935	52.5	5.8	34.5	23.5
	18	13.9	927	33.8	1,380	50.0	5.0	35.0	41.4
	20	16.0	1,098	34.3	1,675	55.0	5.8	36.0	26.5

The calculated control whole blood volumes in the 20 experiments varied from 7.65 to 12.75 per cent of the body weight, the average being 10.26 per cent. The loss of blood which resulted fatally for the morphinized dogs varied from 45 to 61 per cent of the total blood volume, the average being 52.98 per cent. Values for the control (nonmorphinized) animals were almost identical and ranged from 45 to 65 per cent, the average being 51.75 per cent of the total blood volume.

After the systolic arterial blood pressure had been reduced to approximately 70 mm. of mercury by the removal of blood in the various experiments, the average quantity of blood which it was found necessary to remove in order to cause death in the control experiments was 8.83 per cent of the calculated whole blood volume. The corresponding figure for the animals given morphine was 10.4 per cent. This difference may be accounted for by the fact that the control arterial pressures were slightly higher in the nonmorphinized animals.

If one ignores the figures for plasma and whole blood volume and calculates the bleeding volume in terms of percentages of body weight, one finds again that there is little difference in the two groups of experiments. The total quantity of blood that was removed from the morphinized animals varied from 3.64 to 7.30 per cent of the body weight, the average being 5.41 per cent. The bleeding volume of the controls ranged from 4.8 to 7.28 per cent of the body weight, the average being 5.38 per cent. All of the results are given in the table.

COMMENT

Since hemorrhage is probably the most frequent cause of shock in warfare, these experiments were performed in order to try to determine the influence of rather large doses of morphine on the tolerance to bleeding. The dose for a man weighing 70 Kg. corresponding to that used in the experiments would amount to slightly more than 1 grain (0.06 Gm.) of morphine sulfate. Despite the loss of fluid from the intestinal tract which followed the injection of the morphine, the quantity of blood that it was necessary to remove in order to cause death was practically identical with that removed from the controls. It must be emphasized, however, that these experiments were of rather short duration and that morphine may lessen patients' chances of recovery from hemorrhage by causing nausea and interfering with the taking of fluids by mouth.

There is no assurance that these results are applicable to human beings. If they are, they indicate that the chances of withstanding severe hemorrhage are not lessened by the administration of rather large doses of morphine.

The Johns Hopkins Hospital.

ARTERIAL BLOOD SUPPLY OF THE BREAST

REVISED ANATOMIC DATA RELATING TO RECONSTRUCTIVE SURGERY

JACQUES W. MALINIAC, M.D.
NEW YORK

The literature on surgical reconstruction of the breast is surprisingly lacking in adequate descriptions of the blood supply. Many of the procedures in common use appear to have been developed without regard for the preservation of vascularization.[1] Still others are based on a concept of the blood supply which more recent studies prove to be erroneous. Yet preservation of the arterial blood supply is one of the most essential factors in the success of mammaplasty.

The breast is a highly vascular organ. Its surgical reconstruction requires wide undermining of skin flaps, excision of large masses of fat and glandular tissue, with rotation and fixation of the remaining parts. In the course of the operation a number of vessels are likely to become severed or twisted, with resultant interference with vascularization. When there is accurate knowledge of the vascular anatomy this contingency can be avoided.[2] The following factors are of major interest to the surgeon in this connection:

1. Main types and variations in vascularization of the breast.

2. Relationship of the arteries and their branches to the most vulnerable parts of the breast, namely, the areola and the nipple. (This discussion is limited to the arteries, since the veins usually follow the same course.)

3. The depth at which the main vessels and their ramifications are situated with regard to the cutaneous covering and to the gland proper.

4. Symmetry of the vascularization of the breasts.

HISTORICAL DATA

From the point of view of blood supply, the mammary gland can be considered a well nourished organ of the skin. Its developmental history justifies inclusion of the arteries of the breast among the cutaneous arteries.

In 1889, Manchot described the vascularization of the breast in a monograph entitled "Cutaneous Arteries of the Human Body," which was long considered a classic exposition of the subject.[3] According to him the main sources of blood supply are (1) the internal mammary artery, (2) the thoracic lateral artery and (3) the third to the seventh intercostal artery (from the aorta). The main blood supply of the breast, according to Manchot, is provided by six or seven branches of the internal mammary artery, the principal one passing through the second intercostal space. The nipple receives its blood supply only from the internal

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Read in part before the American Society of Plastic and Reconstructive Surgery.

1. Maliniac, J. W.: The Pendulous Hypertrophic Breast: Comparative Values of Present-Day Methods of Repair and the Procedure of Choice, Arch. Surg. **31**:587 (Oct.) 1935.

2. Maliniac, J. W.: Prevention of Necrosis in Plastic Repair of the Breast, Am. J. Surg. **26**:292, 1934.

3. Manchot, C.: Die Hautarterien des menschlichen Körpers, Leipzig, F. C. W. Vogel, 1889.

mammary artery and the intercostal arteries. Participation of the thoracic lateral artery in the supply of the mammary gland and the nipple is minimized as to the former and denied as to the latter (fig. 1).

In spite of the thoroughness of Manchot's anatomic descriptions, his conclusions were faulty. Anatomic dissection alone was insufficient to reveal the smaller

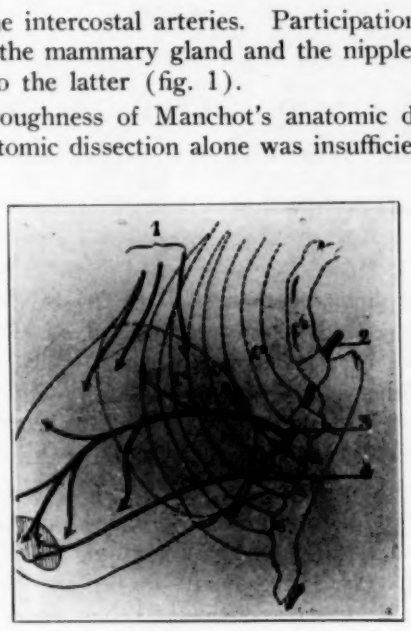

Fig. 1.—Diagrammatic representation of the blood supply of the right breast (Kaufmann). This diagram, although frequently reproduced in textbooks, has been definitely proved inaccurate. *1*, cutaneous branches originating from the axillary artery, which supposedly do not participate in the blood supply of the gland proper; *2*, internal mammary artery; *3*, the main perforating artery supplying the gland and nipple; *4*, secondary perforating artery of the gland. C^1, C^2, C^3 and C^4 are the respective ribs. For comparison, see figures 7 and 10.

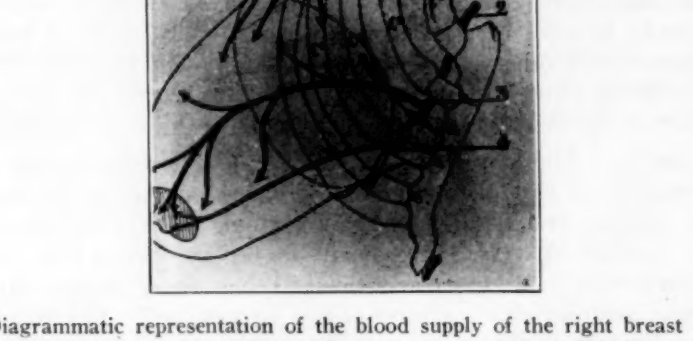

Fig. 2.—Mammaplasty by Biesenberger[14]: *A*, resection of external half of the breast by this procedure totally eliminates the thoracic lateral artery from the blood supply of the remaining gland. In instances in which the thoracic lateral artery is the predominant artery (fig. 7 *B*) and in cases of radial distribution of the periareolar plexus (fig. 10 *C*), the nipple will be deprived of adequate blood supply and necrosis is likely to result. *B*, in addition, upward rotation of the lower pole of the remaining gland is liable to cause torsion of the remaining vessels and thus further interfere with the blood supply.

ramifications observed by later investigators in roentgenograms of injected vessels. In the meantime, however, a number of anatomists accepted and perpetuated Manchot's description of the vascularization of the breast.

Thus, Rauber [4] stated that the blood supply is provided by the internal mammary artery and the intercostal arteries. Spalteholz [5] and later Kaufmann [6] also maintained that the thoracic lateral artery supplies only the cutaneous blood vessels of the breast. On the other hand, Testut [7] described the thoracic lateral artery as participating in the blood supply of both the gland and the nipple.

Insufficient knowledge of the blood supply had important surgical consequences. Particular attention is directed to a paper by Kaufmann,[6] which was responsible for the highly questionable procedures of resection of the external half of the breast. This was performed on the assumption that the thoracic lateral artery did not participate in the vascularization of the mamilla and could therefore be sacrificed without danger of necrosis (fig. 2).

Kaufmann's report, presented before the Anatomical Society of Paris in 1933, was severely criticized by Rouvière,[8] professor of anatomy at the University of Paris. The latter declared, on the basis of the recognized distribution of the lymphatics in this area and the fact that the blood vessels and lymphatics usually follow approximately the same route, that the thoracic lateral artery participates largely in the blood supply of the mammary gland, and in that of the nipple.

As will be shown later, the observations of subsequent investigators confirm Rouvière's statement.

METHODS OF INVESTIGATION

According to some anatomists, an accurate study of the mammary arteries requires the procurement of material from youthful subjects, because after the menopause the breasts become atrophic and the vessels diminish considerably in volume and are not easily penetrated by the injected material. The younger female cadaver, however, is not easily obtainable for study. This may explain some of the contradictory interpretations by different workers. Faulty injections of the vascular system are another cause of erroneous conclusions. In order to obtain accurate data, it is necessary to approach the normal mechanical condition of the living subject and inject the contrast medium into the cadaver through the left carotid artery. Certain of Kaufmann's roentgenograms show that some of the arteries were incompletely filled (fig. 3).

Salmon [9] carried out his work on 14 adult female breasts. He employed dissection and injection of a contrast medium into the cadaver through the left carotid artery.[10] Two types of roentgenologic studies were made, one of the breast with its cutaneous covering and the other of the breast deprived of the skin. Differentiation between the arterial blood supply of the gland proper and the extraglandular vascularization was thus made possible.

Gitis and Livshits [11] based their conclusions on the study of injected blood vessels in 46 female breasts.[12]

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4. Rauber, A. A.: Lehrbuch der Anatomie des Menschen, ed. 14, Leipzig, Georg Thieme, 1932-1938.

5. Spalteholz, W.: Handatlas der Anatomie des Menschen, ed. 12, Leipzig, S. Hirzel, 1937.

6. Kaufmann, R.: Artères de la glande mammaire chez la femme, Ann. d'anat. path. **10**:925, 1933.

7. Testut, J. L.: Traité d'anatomie humaine, ed. 8, Paris, Gaston Doin, 1928-1931.

8. Rouvière, in discussion on Kaufmann.[6]

9. Salmon, M.: Les artères de la peau, Paris, Masson & Cie, 1936, p. 137.

10. The following material was used for injection: linseed oil, 600 Gm.; powdered colophane, 1,000 Gm.; crystallized phenol, 500 Gm.; lead tetroxide, 2,500 Gm.; ether, 500 Gm.

11. Gitis, M. K., and Livshits, D. L.: Arterial Supply of the Female Breast, Sovet. khir., 1936, no. 6, p. 981.

12. The materials for injection were: (1) a suspension of lead tetroxide, liquid petrolatum and turpentine oil, (2) a suspension of official (Russian) mercurial ointment in turpentine oil and (3) a mixture of lead tetroxide in celloidin.

In addition to roentgenographic studies, all investigators used anatomic dissection. The most comprehensive research along this line was done by Marcus,[13] who examined 53 breasts removed together with the underlying muscular and bony tissue of the chest. He injected the arteries with Teichmann's mixture and left strips of skin along the blood vessels to determine their depth. His procedure was as follows: Vertical and horizontal lines were drawn from the sternoclavicular joint, and both lines were subdivided into centimeters, a coordinating system being established in which the contour of the areola and nipple as well as the course of the vessels was outlined. For practical use, a coordinating chart was drawn on a cellophane sheet which was attached to the mammary gland. Following a thorough study of the surface, a sagittal section of the breast was made in order to ascertain the presence of perforating branches (fig. 4).

As a result of these experimental studies, based on examination of 113 breasts, certain definite data on the vascularization of the breast became available, with

Fig. 3.—Roentgenogram of the injected vessels of the breast which served as basis for the diagram in figure 1. The lack of anastomotic branches between the two main vascular pedicles and around the areola is due to faulty injection technic. (From Kaufmann.[6])

only minor variations cited by different investigators. These data will be considered in relation to the factors previously cited as of special interest to the surgeon.

COMMON TYPES OF, AND VARIATIONS IN, VASCULARIZATION OF THE BREAST

The blood supply of the breast is extremely abundant and is provided by three main sources: (1) the internal mammary artery, deriving from the subclavian artery (figs. 5 and 6); (2) the thoracic lateral artery, originating from the axillary artery (fig. 7); (3) the intercostal arteries (aorta), of secondary importance (figs. 4 and 8).

13. Marcus, G. H.: Untersuchungen über die arterielle Blutversorgung der Mamilla, Arch. f. klin. Chir. **179**:361, 1934.

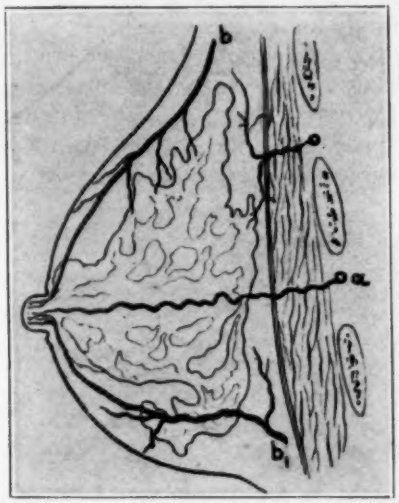

Fig. 4.—Diagram showing the depth of the arteries: *a*, perforating branch of the internal mammary artery penetrating through the entire thickness of the gland to terminate in the nipple; *b* and b_1, ramifications of the main arteries, located at different depths depending on the distance from the nipple as well as on the amount of subcutaneous fat. In the region of the areola the vessels form a periareolar arterial and venous plexus in intimate contact with the skin and gland proper. b_1, on the outer aspect of the breast, is at a deeper level than *b*, on the inner aspect, because of the presence of more adipose tissue on the external side.

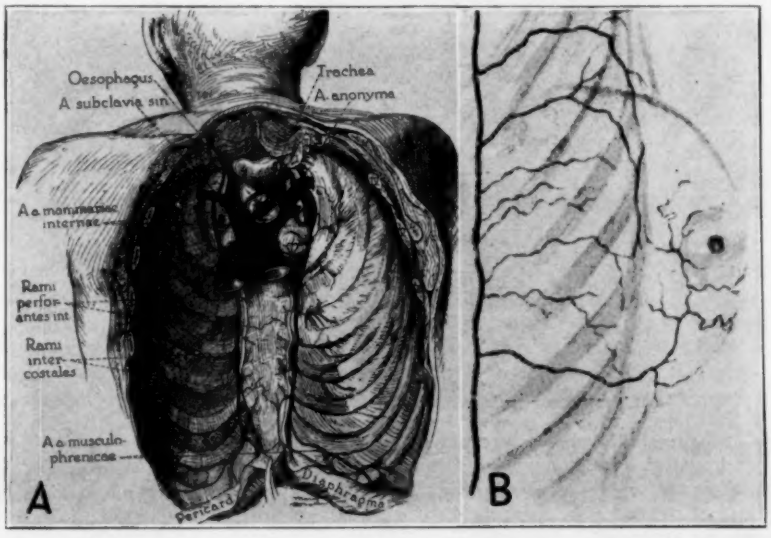

Fig. 5.—*A*, origin of internal mammary artery. The subclavian arteries, from which the internal mammary arteries originate, are shown on the inner aspect of the thoracic wall. Points at which the main perforating arteries pass through the intercostal spaces are indicated by arrows. (From Anson, B. J.; Wright, R. R., and Wolfer, J. A.: Blood Supply of the Mammary Gland, *Surg., Gynec. & Obst.* **69**:468, 1939.) *B*, the injected internal mammary artery, showing the treelike ramification, consisting of five to seven branches having their origin in the deeper segment of the artery. These branches anastomose in an arch-shaped manner; most of them are subdivided along the mammary gland, sending ramifications to the thoracic lateral artery (Gitis and Livshits [11]).

The degree of participation of these different sources in the vascularization of the gland, skin and nipple varies. It is important therefore, to consider the basic type and the variations for each source.

Vascularization takes place through at least two, and often three, main sources. The most frequent combinations are: (1) the internal mammary artery and the thoracic lateral artery (50 per cent); (2) the internal mammary artery and the intercostal arteries (30 per cent); (3) the internal mammary artery, the thoracic lateral artery and the intercostal arteries (aorta) (18 per cent).

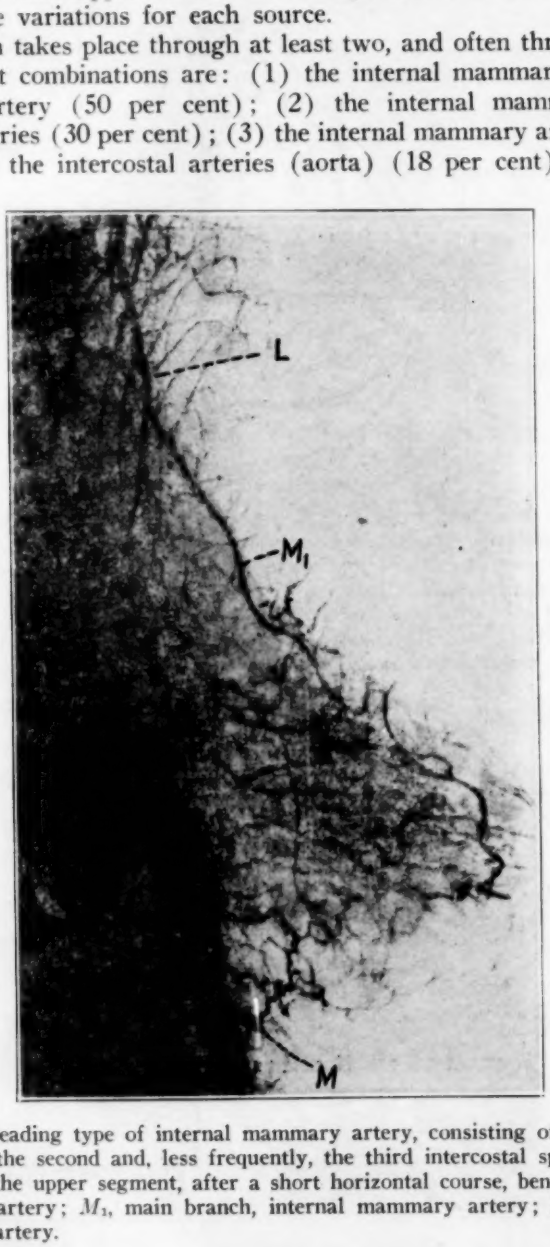

Fig. 6.—The spreading type of internal mammary artery, consisting of a few ramifications perforating mainly the second and, less frequently, the third intercostal space. The large perforating branch in the upper segment, after a short horizontal course, bends toward the nipple. *L*, thoracic lateral artery; M_1, main branch, internal mammary artery; *M*, posterior branch, internal mammary artery.

Combination of the thoracic lateral and the intercostal arteries, without the internal mammary artery, has not been encountered (table 1).

I. THE INTERNAL MAMMARY ARTERY (FIG. 5A)

The internal mammary artery has its origin in the subclavian artery in the neck and descends into the thorax behind the clavicle and the costal cartilages to the sixth intercostal space, where it is divided into its terminal ramifications.

Two types of branches are to be considered: namely, the anterior perforating and the posterior (with respect to the gland).

A. The Anterior Perforating Branches (figs. 5 *B* and 6).—The internal mammary artery sends perforating branches, usually six to eight, through the first to the fourth intercostal spaces—most frequently through the second, rarely through the first and fourth. From these perforating branches are derived the intercostal ramifications which run along the edges of the ribs, supplying the skin and muscles; the perforating branches become the main arteries of the gland.

The location of the main perforating branches is of definite practical import. When their origin is in the upper thoracic segment, the branches turn caudally toward the nipple after a short horizontal course. When their origin is deeper, the main artery branches out in a treelike manner (fig. 5 *B*).

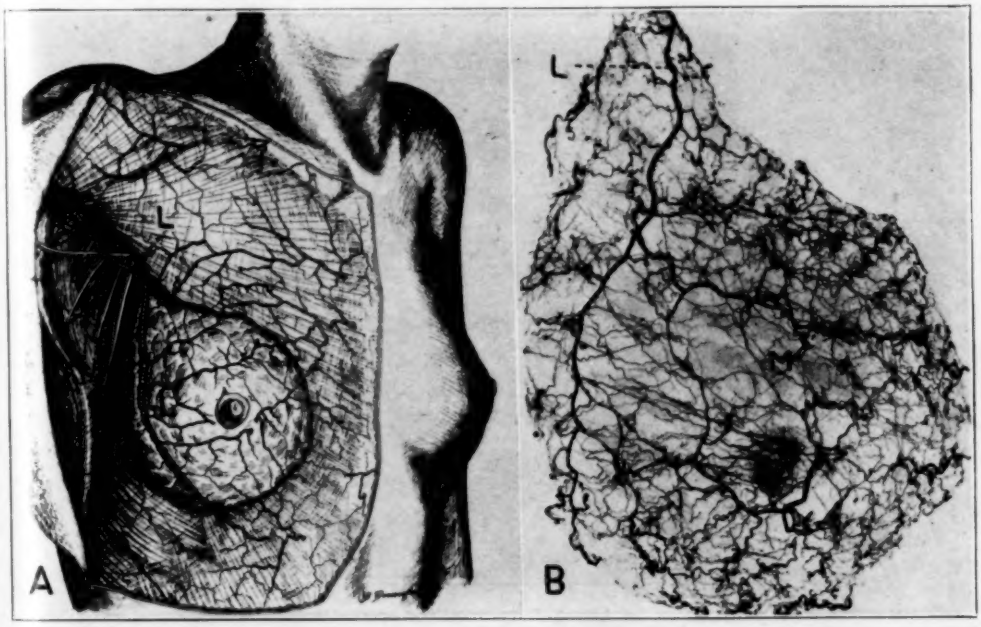

Fig. 7.—*A*, thoracic lateral artery and its topography (Salmon [9]). It originates from the external mammary artery and rarely from the axillary artery. Two main branches follow the external aspect of the gland. Note the numerous anastomoses above and below the nipple with the branches of the internal mammary artery. Its extraglandular topography, anterior to the neurovascular pedicle of the musculature, is shown. *L*, thoracic lateral artery. *B*, this figure represents the injected right breast of a young woman of 22, deprived of cutaneous covering and adipose tissue (Salmon [9]). The thoracic lateral artery (*L*) here is unusually well developed and by itself supplies more than half of the gland. The main perforating branch of the internal mammary artery (*M*) is small, only slightly larger than the other branches of the artery. Resection of the external half of the breast in this case would in all likelihood sufficiently disturb the blood supply of the nipple to bring about necrosis.

Two main types of variations are observed in the internal mammary artery. In the first, a few ramifications, perforating mainly the second and less frequently the third and fifth intercostal spaces, constitute the "spreading" type (fig. 6). Here the large perforating branch in the upper segment, after a short horizontal course, bends downward toward the nipple. From the angulation anastomotic branches are directed toward the external mammary artery. The main branch, at various distances from the nipple, sends out ramifications surrounding the

areola in the upper lateral and lower medial quadrants, forming an anastomotic ring. The second type is characterized by five to seven perforating branches, having their origin in the deeper segment of the artery. These branches form arch-shaped anastomoses. Most of the branches are subdivided along the mammary gland, sending numerous ramifications toward the thoracic lateral artery (fig. 5 *B*). A third intermediate type is sometimes observed in which types 1 and 2 are present.

B. The Posterior Perforating Branches (fig. 8).—The posterior aspect of the breast is approached by two or three arterial ramifications, mostly along the inner half of the gland. These branches are often wrongly considered as being derived from the aorta: anatomic studies consisting of careful roentgenographic examination of the injected vessels and dissection reveal that they arise from the internal mammary artery. Their disposition in the retromammary space and their origin are important in the evaluation of the posterior approach to the gland.

Fig. 8.—Same preparation as in figure 7 *A*, showing posterior aspect of breast. Note that the main retromammary arteries originate from the internal mammary artery. These arteries are long and penetrate the gland by short ramifications. This disposition permits easy retraction of the vessels in this area. *M*, internal mammary artery; *L*, thoracic lateral artery; *I*, intercostal artery (aorta); *IM*, inner intercostal artery (internal mammary artery).

One of these branches passes through the fourth intercostal space and the other through the fifth. They reach the posterior surface of the gland in the following way: The upper branch perforates the breast from behind forward and reaches the anterior aspect, where it anastomoses with the branches of the thoracic lateral artery. The inferior branch is long and sends short ramifications into the gland; it is easily retracted during exposure of the gland's posterior aspect.

II. THE THORACIC LATERAL ARTERY

Descriptions of this vessel vary greatly. The resultant incorrect deductions are responsible for some of the surgical procedures which deprive the gland of its essential blood supply [14] (fig. 2).

14. Biesenberger, H.: Eine neue Methode der Mammaplastik, Zentralbl. f. Chir. **57**:2971, 1930.

As a rule the size of the thoracic lateral artery is dependent on the development of the internal mammary artery (fig. 7 *B*). Although the majority of authors agree in principle as to the important role of the latter in vascularization of the breast, similar agreement does not seem to prevail with regard to the thoracic lateral artery. Rouvière, one of the outstanding anatomists of the present day, pointed out that the extensive development of the mammary lymphatics and the close parallelism in the development of the lymphatic, venous and arterial systems indicate that the thoracic lateral artery participates abundantly in the vascularization of the central parts of the gland. This contradicts the views of Manchot and his followers, who maintained that the thoracic lateral artery scarcely participates in the blood supply of the gland and does not provide branches for the nipple. Undoubtedly more reliance can be placed on the findings of later

TABLE 1.—*Distribution of the Main Arteries of the Breast* *

Main Arteries	Origin	Main Types of Ramifications	Extent of Participation	Region Supplied	Depth	Periareolar Circulation
Internal mammary artery (figs. 5*B*, 6 and 8)	Subclavian artery	(1) 5 to 8 perforating branches; (2) one main branch through 2d or 3d intercostal space	Largest in size and length; constant participation	Main blood supply of gland in majority of cases	0.5 to 1 cm. subcutaneously depending on amount of fat present	Predominant in vascularization of areola and nipple in majority of cases
Thoracic lateral artery (fig. 7)	External mammary artery; rarely originates directly from the axillary artery	Two parallel branches on lateral aspect of breast	Second in size, varied, depending on development of internal mammary artery; in 13 per cent of cases predominant in vascularization of gland and nipple	External half of breast; maintains balance with internal mammary artery	1 to 2.5 cm. depending on amount of fat on external aspect	In 13 per cent of cases constitutes main supply to areola and nipple
Intercostal arteries (figs. 4 and 8)	The inner group originates from the internal mammary artery, the outer group from the aorta	The inner group has 2 to 3 ramifications to the posterior aspect of the gland; the outer group is less important	Anastomotic plexus in lower quadrants mostly on account of inner intercostal arteries; a main perforating branch directly into the nipple is often present	Lower quadrants; sometimes areola and nipple through a direct perforating branch	Retromammary space	Mainly through a direct perforating branch

* These data are based on dissection and study of roentgenograms of injected vessels in 104 female breasts.

investigators, like Rouvière, who could visualize the fine branches of the anastomotic plexuses of the gland and nipple by roentgenographic studies.

Marcus [13] revealed that the thoracic lateral artery participates in vascularization of the nipple in 55 per cent of cases and of the gland in 68 per cent (table 1).

Gitis and Livshits [11] found constant participation of the thoracic lateral artery in the vascularization of the skin, gland and nipple. They stated that the size of the artery varies and is frequently dependent on the development of the internal mammary artery.

The thoracic lateral artery, also called the principal external artery, takes its origin from the external mammary artery, a branch of the axillary. It rarely is derived from the axillary artery (fig. 7 *A*).

In its extraglandular course the thoracic lateral artery is situated anterior to the perforating branch of the third intercostal nerve and the neuromuscular pedicle. When it arises from the external mammary artery, as occurs most frequently, it rapidly abandons the posterior aspect of the pectoral muscle.

Its caliber varies from 1 to 2 mm., according to the size of the gland. It is directed obliquely downward, inward and forward from the axilla, first toward the axillary prolongation of the gland and then following its anterior aspect, often in contact with the gland near the external border and terminating at the lower level of the gland in its final branches. This area is rich in subcutaneous fat and is abundantly vascularized.

The common type shows two branches which run parallel to the lateral aspect of the gland. One branch is always more developed than the other. The medial branch is deflected toward the medial side near the nipple to form an anastomosis with branches of the internal mammary artery. The lateral branch turns medially below the nipple, and usually sends branches into the nipple directly or through anastomosis with other arteries (fig. 7 *A*).

Terminal branches consist of two or three ramifications which often penetrate into the gland and pass under the nipple for anastomosis with the intercostal arteries.

III. INTERCOSTAL ARTERIES

There is a lack of agreement as to the origin of the intercostal arteries which supply the breast. Salmon [9] considers the inner intercostal arteries, which penetrate the fourth and fifth intercostal spaces, as posterior branches of the internal mammary artery (fig. 8). Only the external intercostal arteries originate in the aorta and their glandular ramifications are not very numerous, varying in size and direction. They are located on the pectoral aponeurosis at the external aspect of the gland and form an anastomotic plexus in the lower quadrant with the ramifications of the internal mammary artery on the inside and of the thoracic lateral artery on the outside. From this plexus derive branches going toward the areola and nipple. As a rule, however, external intercostal arteries do not participate to a great extent in the blood supply of the gland and nipple, unlike the inner intercostal arteries, deriving from the internal mammary artery. To the latter group also belongs an intercostal perforating branch, not always present, which penetrates through the entire depth of the gland, enters the nipple directly and fans out around the areola (fig. 4). The intercostal arteries do not interfere with the easy separation of the gland from the retromammary space, as they usually run along the pectoral fascia and show short terminal branches.

RELATIONSHIP OF THE MAIN SOURCES OF BLOOD SUPPLY TO THE AREOLA AND NIPPLE

The central portion of the breast is particularly liable to necrosis in certain surgical procedures. It is therefore important to consider the topography of the vascular ramifications in this area (fig. 10).

The branches of the three main sources of blood supply, in approaching the gland, form two anastomotic plexuses, one superficial and the other in the depths of the gland. From these two plexuses ramifications extend toward the surface and the base of the nipple and the areola. There are many variations in these periareolar anastomoses, and certain basic types and abnormalities can be discerned. Their comprehension is essential to safe surgical intervention in this region.

I. CIRCULAR PERIAREOLAR PLEXUS (FIG. 10A)

In this group the ramifications form a nearly complete ring around the nipple. The width of the ring varies between 2 and 5 cm.; it is formed by ramifications of the internal mammary artery in the inner upper angle, the thoracic

lateral artery at the outer upper angle and the intercostal arteries below. The branches of the internal mammary artery, which predominate, are divided at different distances from the nipple into two ramifications which encircle it, together with branches from the other sources. From this vascular ring fine arterioles reach the base of the nipple and the areola. This type of vascularization assures the maximum blood supply and can be considered the safest from the viewpoint of possible necrosis. It was found in 70 to 74 per cent of the breasts examined (table 2). Resection of the external half of the breast will not compromise the vitality of the nipple in the presence of circular periareolar vascularization. This is particularly true in cases in which the thoracic lateral artery participates but slightly in the formation of the plexus.

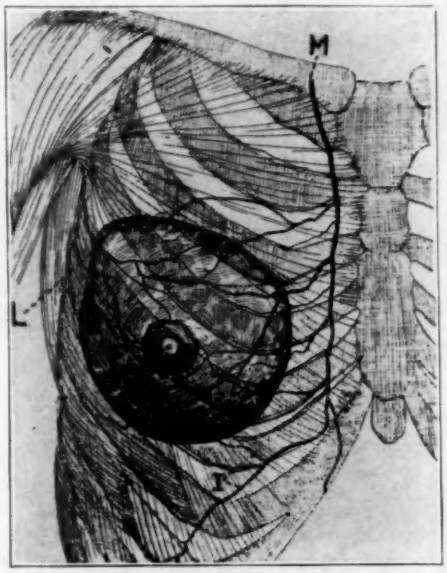

Fig. 9.—Diagram of the main vascular pedicles of the breast illustrating the present concept of its blood supply. Note the numerous anastomotic branches between the two main vessels and the periareolar plexus. The deeply located parts of the arteries are represented in dotted lines. *M*, internal mammary artery; *L*, thoracic lateral artery; *I*, intercostal arteries.

TABLE 2.—*Varieties in Periareolar Vascularization*

Type	Origin	Ramifications	Relationship to Surgery	Frequency
1. Circular plexus (fig. 10*A*)	Usually the two main sources with predominance of the internal mammary artery	Assure maximum blood supply to nipple by extensive circular anastomosis	Safest	70 to 74 per cent of cases
2. Loop plexus (fig. 10*B*)	Thoracic lateral artery predominant; participates with other sources of blood supply to formation of a loop	Derive mostly from the thoracic lateral artery	Extensive lateral resection of the gland may deprive the nipple of adequate circulation and result in necrosis	20 per cent of cases
3. Radial plexus (fig. 10*C*)	Lack of anastomosis between two main sources: thoracic lateral artery and internal mammary artery	Characterized by absence of anastomotic branches between the main sources of blood supply	Deep periareolar incision will result in necrosis of corresponding part	6 per cent of cases

II. LOOP TYPE PLEXUS (FIG. 10B)

This is observed when the thoracic lateral artery is the most developed. Its branches turn medially above and under the nipple, anastomosing with the ramifications of the lesser sources of blood supply. The periareolar plexus originates from this loop.

This type has been observed in about 20 per cent of the breasts examined. Extensive resection of glandular tissue vascularized by the thoracic lateral artery may result in necrosis of the central parts of the gland (table 2).

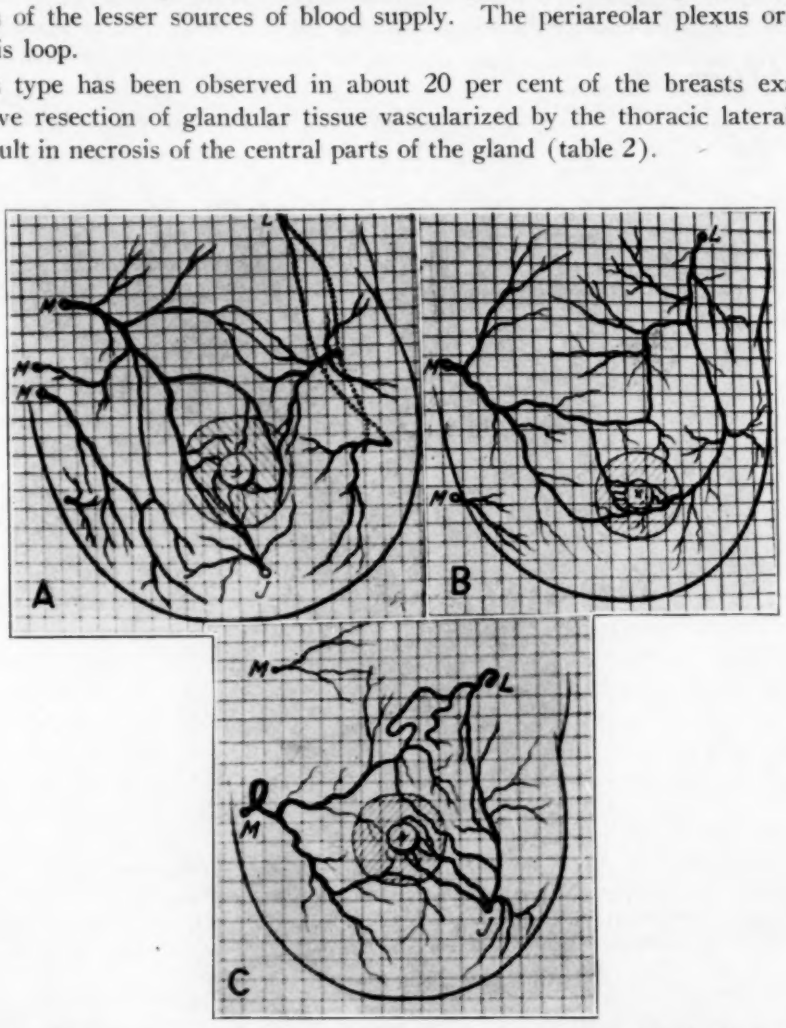

Fig. 10—*A*, circular periareolar plexus (Marcus [13]). The ramifications of the main arteries form a complete ring around the nipple. This type of vascularization assures maximum blood supply and is the safest from the viewpoint of possible necrosis. It is found in about 70 to 74 per cent of cases. The internal mammary artery is well developed. Resection of the external half of the breast, sacrificing the thoracic lateral artery, will not compromise here the vitality of the central portion of the gland. *M*, internal mammary artery; *L*, thoracic lateral artery; *J*, intercostal arteries. *B*, the loop type of periareolar plexus, observed when the thoracic lateral artery is predominant. The branches from both sources anastomose above and below the nipple, forming a loop. This type is found in about 20 per cent of cases. Wide external resection of the gland is liable to disrupt the blood supply of the central portion. *M*, internal mammary artery; *L*, thoracic lateral artery. *C*, radial type of periareolar plexus. This type is characterized by the lack of any ring or loop formation around the nipple. The ramifications of the main arteries are directed toward the nipple without anastomosis between them and their arterial pedicles. This type of plexus is found in 6 per cent of cases. Resection of any extensive amount of the lateral part of the breast will unavoidably be followed by necrosis of the nipple. *M*, internal mammary artery. *L*, thoracic lateral artery; *J*, intercostal artery.

III. RADIAL TYPE PLEXUS (FIG. 10C)

This is the least frequent type, observed in about 6 per cent of the total number of breasts. It is characterized by lack of any ring or loop formation around the nipple. The ramifications from the two main sources are directed toward the nipple at a distance from each other without anastomosis between them and their main arterial pedicles. With this type of plexus a deep circular incision in the areolar zone will necessarily sever the main sources of blood supply to the corresponding parts of the breast. An exception might occur if the perforating intercostal artery (branch of the internal mammary artery) reached the nipple directly from the posterior aspect of the gland (fig. 4). This branch, however, is not always present, and in fact was usually observed to be missing in the radial type of ramification.

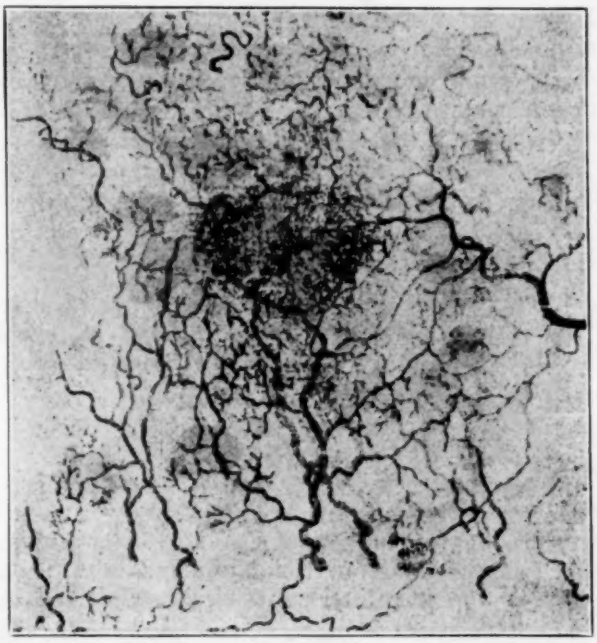

Fig. 11.—Disposition of the venous and arterial plexus around the areola. This plexus is highly developed and superficially located between the skin and gland proper without presence of fat. The preservation of these two plexuses is essential for avoidance of necrosis and requires superficial dissection of skin when transposition of the nipple is done.

As it is impossible to foresee which type of vascularization will be encountered, all types must be kept in mind in evaluating any reconstructive procedure.

DEPTH OF THE VESSELS IN RELATIONSHIP TO THE CUTANEOUS COVERING AND THE GLAND PROPER

The mammary vessels, as derivatives of cutaneous arteries, are located in the subcutaneous layer. Their depth depends on the amount of fatty tissue present: in fatty hypertrophies they are found at a deeper level than in the atrophic types (fig. 4). As the mammary arteries are tortuous, they permeate the perimammary fat at various levels, and are accompanied in their trajectories by corresponding veins and lymphatics.

1. The origin of the main perforating branches of the internal mammary artery is found at a distance of 1 to 1.5 cm. from the border of the sternum. Anteriorly their ramifications are found at a depth of 0.5 to 1 cm., depending on the thickness of the fat layer. They are often visible under the skin.

2. The main branches of the thoracic lateral artery are usually located at a deeper level, from 1 to 2.5 cm., because of the greater amount of fat present on the external aspect of the breast.

3. In approaching the areolar region, the blood vessels become more superficial and lie closer to the gland. In their course, they send forth arterioles toward the gland and the skin, forming a deep and a superficial plexus. The position of these plexuses is determined by the relationship between the gland and the cutaneous skin covering (fig. 4). In a sagittal section of the normal breast, the cutaneous surface appears half round and the gland cone shaped. The apex of the cone joins the cutaneous surface at the level of the nipple. Thus a heavy fatty layer is present between the gland and the skin at the periphery, gradually thinning out toward the center and disappearing entirely at the level of the areola, where skin and gland are in intimate contact. Here the periareolar plexus is very superficial, being covered only by the fine areolar skin. The preservation of the arterial and venous plexuses is imperative for the prevention of necrosis in this area (fig. 11). Circular incisions made here should be intradermal and the dissection of the skin superficial.

SYMMETRY OF VASCULARIZATION

Most investigators agree that symmetric vascularization of both breasts is rare. This is evident from study of roentgenograms of pairs of breasts. It explains the occurrence of unilateral necrosis where identical surgical procedures are used on both sides (fig. 7 *B*).

SUMMARY AND CONCLUSIONS

Accurate knowledge of the vascularization of the breast is essential to the avoidance of necrosis in mammaplasty.

Most descriptions of the mammary blood supply by older anatomists were based solely on dissection and thus did not reveal the minute vascular ramifications observed by later investigators in roentgenographic studies of injected vessels. The data presented here are based on dissection and roentgenographic studies of injected vessels in 103 female breasts.

The blood supply of the breast is derived from at least two and often three of the following main sources: (*a*) the internal mammary artery, (*b*) the thoracic lateral artery and (*c*) the intercostal arteries (aorta). The most frequent combination is that of the internal mammary artery and the thoracic lateral artery (50 per cent).

A balance is usually maintained between the two main internal and external vascular pedicles. The internal mammary artery is always present. In approximately 55 per cent of the cases the thoracic lateral artery has an equal part with the internal mammary, and in 13 per cent a predominant part, in vascularization of the gland, areola and nipple.

The ramifications of the three main arteries of the breast participate in the formation of a superficial and a deep periareolar plexus, of which there are three basic types:

(*a*) The circular plexus (74 per cent) provides the safest vascularization for the nipple and areola.

(*b*) The loop type (20 per cent) occurs when the thoracic lateral artery is predominant.

(*c*) The radial type (6 per cent) has periareolar ramifications from the two main arteries, directed toward the nipple without anastomoses. Circular incision around the nipple in this type is likely to sever the blood supply and result in necrosis.

As it is impossible, prior to operation, to foresee the type of vascularization present in the living person, all surgical procedures based on wide resections of mammary structures with ligation of large vascular branches must be considered to involve the danger of necrosis.

The surgical procedure of choice must preserve the blood supply in all types of vascularization.

106 East Seventy-Eighth Street.

ADVENTITIOUS BURSAS

RONALD M. BUCK, M.D.
Fellow in Orthopedic Surgery, Mayo Foundation

JOHN R. McDONALD, M.D.*
AND
RALPH K. GHORMLEY, M.D.†
ROCHESTER, MINN.

So-called adventitious bursas are encountered frequently, but a review of the literature indicates that they are poorly understood. Most authors disagree as to the pathogenesis and histologic appearance of such bursas.

In 1890 Schuchardt [1] stated that hygromas could develop anywhere in connective tissue independently of previously formed connective tissue spaces. He explained the formation of subcutaneous hygromas on the basis of inflammation, since he found fibrin in inflamed connective tissue. He thought that the fibrin

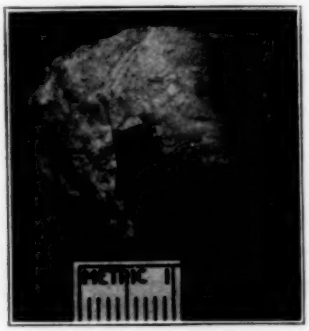

Fig. 1.—Adventitious bursa from the soft tissues over the medial aspect of the head of the first metatarsal bone. The cystic cavity in the center is apparent.

was a part of a liquefaction process that continued until the eventual formation of multilocular small sacs and the subsequent degeneration of the separating walls. He said that the peculiar fibrinous inflammatory process could be recognized in old hygromas only in the wall of the sac and could be followed for a considerable depth. In these regions he found that the nuclei were divided and the cells swollen as they are in coagulation necrosis.

Hammar [2] in 1894 expressed the opinion that the lining of the subcutaneous bursa was connective tissue and not endothelium.

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† Section on Orthopedic Surgery, Mayo Clinic.

Abridgment of a thesis submitted by Dr. Buck to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Orthopedic Surgery.

1. Schuchardt, K.: Ueber die Entstehung der subcutanen Hygrome, Arch. f. klin. Chir. **40**:606-609, 1890.

2. Hammar, J. A.: Ueber den feineren Bau der Gelenke, Arch. f. mikr. Anat. **43**:266, 1894; cited by Jones.[10]

Dömény [3] in 1897 said that superficial bursas developed in a deep loose stratum of subcutaneous tissue and that the connective tissue in the region of embryonic bursas had a peculiar swollen appearance like gelatin. He noted that the olecranon bursa of a baby aged 2 months had two connective tissue spaces under the layer

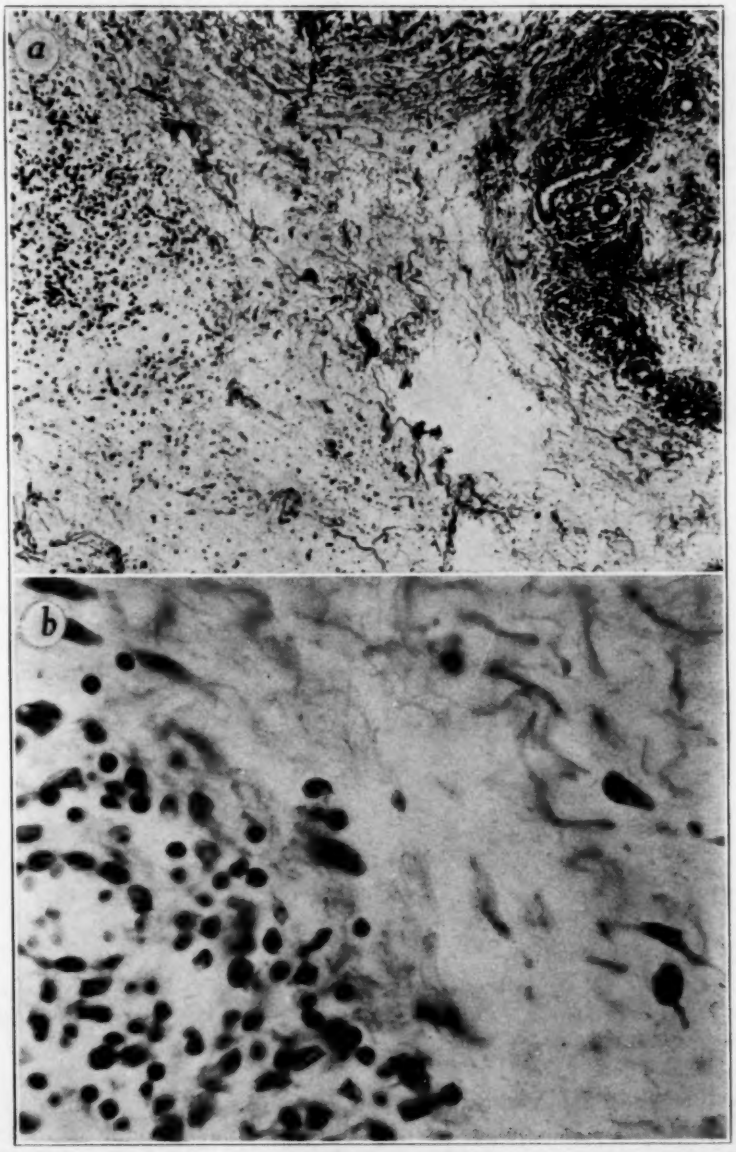

Fig. 2.—Sections of connective tissue in the medial aspect of the first metatarsal bone showing numerous small capillaries and an inflammatory reaction consisting mostly of lymphocytes but situated for the most part in a perivascular arrangement: (*a*) stained with hematoxylin and eosin (× 75); (*b*) stained with hematoxylin and eosin (× 500).

of fat and that the bursa did not become distinct until the fat about the elbow disappeared.

3. Dömény, P.: Entwickelung und Bau der Bursae mucosae, Arch. f. Anat. u. Entwcklngsgesch., 1897, pp. 295-306.

In 1903 Langemak [4] reviewed the existing literature on bursas and disagreed with Schuchardt. He expressed the opinion that the gelatinous material in bursas was purely degenerative instead of a fibrinous exudate. He said that this degenerative material was "fibrinoid" and that the distinguishing feature was that it stained yellow with Van Gieson's stain instead of pink, as connective tissue usually does.

Virchow,[5] as quoted by Churchman,[6] said: "The bursae are in no sense true serous sacs, . . . but are rather places where the connective tissue, originally present in continuo, forms spaces by a process of atrophy and where these spaces come, in time, to be independent cavities."

Clark [7] in 1908 described an adventitious bursa that had been removed from the surface of an amputated hammer toe. He said that a small amount of glairy

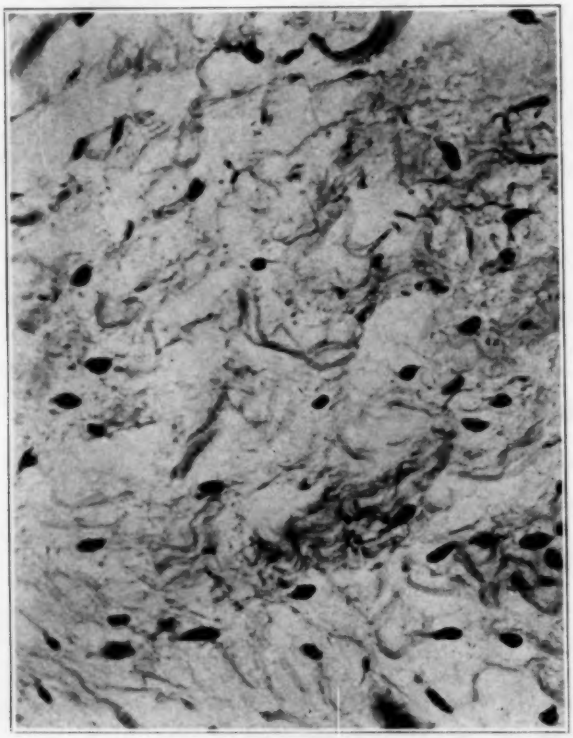

Fig. 3.—Connective tissue from the medial aspect of the first metatarsal bone showing separation of the collagen fibrils, swelling caused by a mucus-like material and also by fibroblasts. (Stained with hematoxylin and eosin [× 365].)

fluid escaped when the bursa was sectioned. The microscopic picture was that of a finely fibrillated tissue supported by a poorly stained framework of connective tissue. He found no nuclei or distinct cell bodies in the lining itself, and the tissue in the lining was similar to tissue frequently seen adjoining regions of cystic degeneration in fibromas.

4. Langemak, O.: Die Entstehung der Hygrome, Arch. f. klin. Chir. **70**:946-972, 1903.

5. Virchow, cited by Churchman.[6]

6. Churchman, J. W.: Luetic Bursopathy of Verneuil, Am. J. M. Sc. **138**:371-396 (Sept.) 1909.

7. Clark, W. C.: The Pathogenesis of Ganglia, with a Description of the Structure and Development of Synovial Membrane, Surg., Gynec. & Obst. **7**:56-78 (July) 1908.

Sutton [8] in 1922 explained the formation of bursas as a rupture of the intermediate connective tissue over a bony prominence. He said that the connective tissue became filled with fluid and the wall was formed by the thickened connective tissue. Hertzler [9] in 1923 discussed the inflammation of deep calcaneal bursas and voiced the opinion that pressure caused the formation of subcutaneous or any other type of bursas.

In 1930 Jones [10] made an extensive study of cystic bursal hygromas and found that the walls of prepatellar bursas consisted of two main layers, an external and an internal. He said that the external layer was composed principally of moderately loose, white fibrous connective tissue including vascular fat lobules. Some

Fig. 4.—The wall of an adventitious bursa from the medial aspect of the first metatarsal bone; the fibroblasts are flattened and there is a concentric arrangement around the bursal cavity. (Stained with hematoxylin and eosin [× 130].)

of the fat lobules showed signs of atrophy with proliferation of young connective tissue. The internal layer was composed of connective tissue, which evidently was proliferating and rich in capillaries. Toward the center of the cavity there were connective tissue cells with a great quantity of collagen fibers between the cells. The nuclei were observed to be necrotic, and degeneration was noted in other regions.

8. Bland-Sutton, J.: Tumours, Innocent and Malignant: Their Clinical Characters and Appropriate Treatment, London, Cassell & Co., Ltd., 1922.

9. Hertzler, A. E.: Inflammation of the Deep Calcaneal Bursa, J. A. M. A. **81**:8-9 (July 7) 1923.

10. Jones, H. T.: Cystic Bursal Hygromas, J. Bone & Joint Surg. **12**:45-89 (Jan.) 1930.

Roberts [11] in 1929 studied the pads of fat over calcaneal spurs and observed that the masses of fat were surrounded by delicate stromas of connective tissue which were grouped together by membranous partitions, so that a loosely connected layer was formed in which the spaces seemed to be filled with lymph. He accepted the theory that bursas are enormously distended lymph spaces.

EMBRYOLOGIC ASPECTS

Material.—The material for this study was secured from specimens removed at the time of plastic repair of the head of the first metatarsal bone for hallux valgus deformity and bunions. Approximately 270 specimens were examined, and

Fig. 5.—Adventitious bursa from the medial aspect of the first metatarsal bone. The wall of the cavity contains swollen fibroblasts with mucoid or myxomatous degeneration; the central portion is practically acellular and is made up of a homogeneous staining mucoid material. (Stained with hematoxylin and eosin [× 50].)

sections of bursas were taken when they were present. Bursas were found in all stages of development; some contained large cystic cavities (fig. 1); others contained small cavities, and still others contained none at all. Included in this series was one bursa of the external malleolus and one removed from the foot. For comparison, several prepatellar bursas were examined. One specimen of a true bursa removed from the popliteal space was studied.

On all tissue studied, the following stains were used: hematoxylin and eosin, mucicarmine, the Mallory-Heidenhain aniline blue stain, Van Gieson's stain and elastin H.

11. Roberts, P. W.: Bursitis of the Foot: A Neglected Cause of Disability, Am. J. Surg. **6**:313-317 (March) 1929.

Results.—The histologic changes which were found in these adventitious bursas of the feet may be classified as early and late. Early changes can arbitrarily be taken as those which are apparent in the connective tissue of the affected region but which have not resulted in the formation of actual liquid mucoid material. Late changes are those which have resulted in the formation of an actual cavity which contains the mucoid material typical of bursas.

In the region surrounding beginning or early bursal formation, an increased number of blood vessels constantly was present in the conective tissue. These vessels consisted of small capillaries. In and around these newly formed blood vessels were usually to be found numerous lymphocytes and occasionally a polymorphonuclear leukocyte (fig. 2).

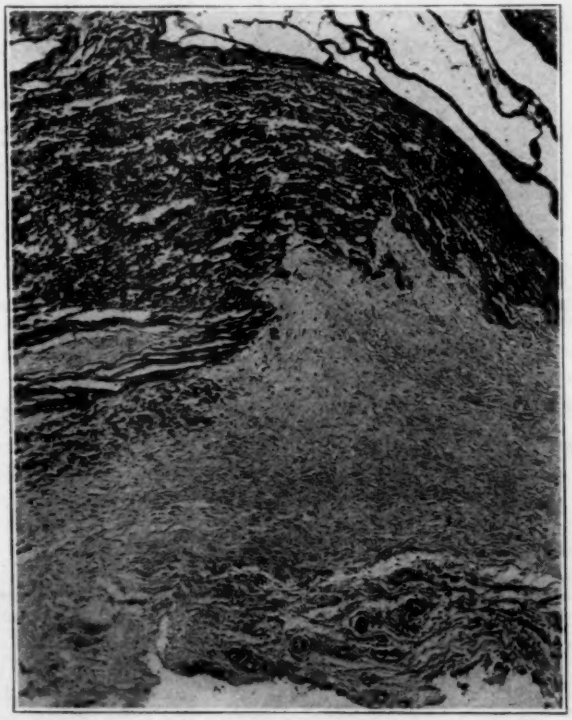

Fig. 6.—Adventitious bursa from the medial aspect of the first metatarsal bone stained with mucicarmine stain, showing affinity of the mucoid material in the cavity for carmine (×45).

The fibroblasts and collagen fibrils in the vicinity where the bursal cavity was about to form became swollen and separated by a mucus-like material which stained not at all or, at the most, faintly bluish with hematoxylin and eosin and contained no cells (fig. 3). The collagen in this region did not stain as strongly reddish with Van Gieson's stain as did the collagen fibrils peripheral to this region. The results of staining with mucicarmine were negative at this stage.

In sections of well formed adventitious bursas, that is, those in which there was an actual cavity filled with mucoid material, the new blood vessels and the inflammatory cells were evident in the connective tissue of the wall of the cyst. Toward the cavity, the myxomatous or mucoid degeneration became more marked. The fibroblasts and collagen fibrils became more swollen and finally disappeared. The fibroblasts and collagen fibrils which remained around the cavity assumed

a flattened appearance and were arranged concentrically (fig. 4). The central mucoid material in the cyst contained no collagen fibrils and no cells (fig. 5). In the vicinity of the cystic cavity the collagen fibrils eventually lost their affinity for the fuchsin in the Van Gieson stain. As more mucoid material formed between

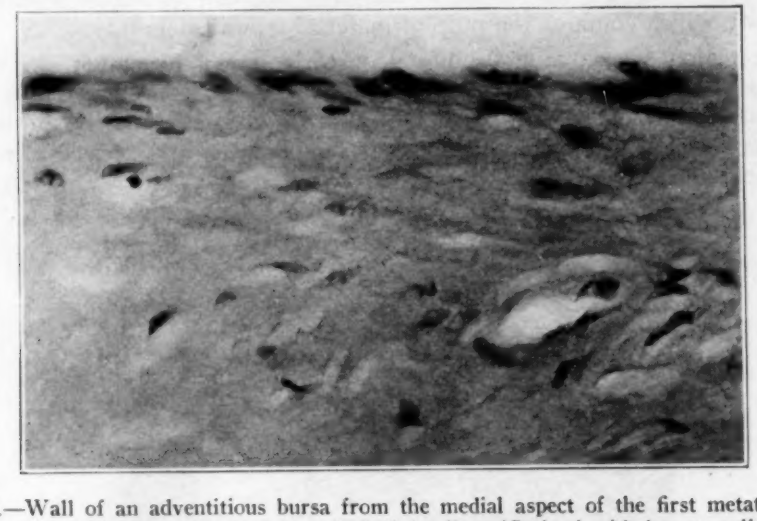

Fig. 7.—Wall of an adventitious bursa from the medial aspect of the first metatarsal bone. The flattened fibroblastic cells simulate endothelial cells. (Stained with hematoxylin and eosin [× 300].)

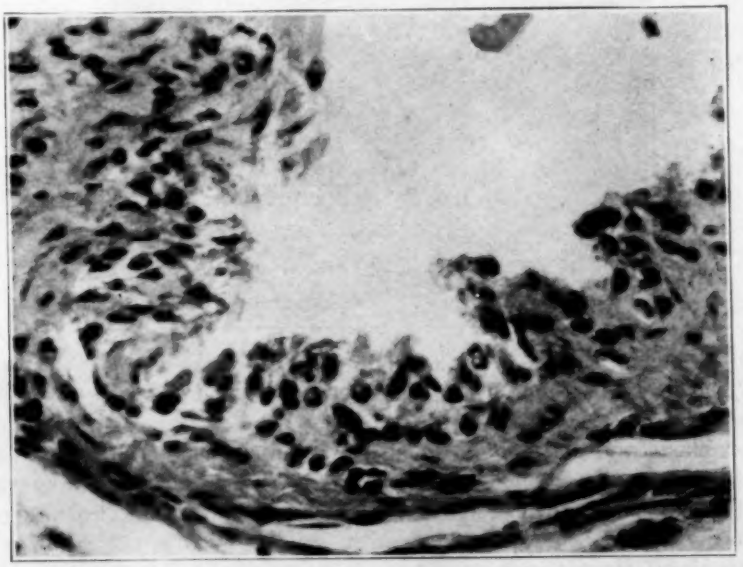

Fig. 8.—True bursa from the popliteal space. The lining endothelial cells are thrown in folds; there is no mucoid or myxomatous degeneration of the connective tissue in the wall of the cavity. (Stained with hematoxylin and eosin [× 420].)

the connective tissue fibrils, the mucicarmine stain became slightly positive, until in the central cystic region it was very strongly positive (fig. 6). In no specimen of these adventitious bursas could lining cells be found which could be interpreted

as endothelial cells. In certain specimens where well formed cysts were apparent, flattened cells lined the cavity. It would appear to be more logical to consider these as flattened fibroblastic cells than as endothelial cells (fig. 7).

The histologic study of the prepatellar bursas revealed throughout exactly the same changes observed in the adventitious bursas obtained from bunions. Evidently they also are adventitious, not true bursas. In contrast, a bursal cavity removed from the popliteal space was lined with endothelial cells which were very distinct and arranged in a villous formation suggestive of synovial lining (fig. 8). There was no evidence of myxomatous or mucoid change in the connective tissue surrounding the endothelium. Van Gieson's stain revealed that the collagen fibrils were plentiful surrounding bursas. The mucicarmine stain revealed small amounts of mucus-like material in the lining cells. The probabilities are that the bursal cavity was directly connected with the knee joint. The connection is suggested by the similarity between the lining endothelium of this bursa and the synovium of the joint.

COMMENT

This study was undertaken in order that the development and pathogenesis of adventitious bursas might be better understood. As found in most of the textbooks, the definition of a bursa is inconstant and the meaning and description not clear.

In the development of adventitious bursas, it would appear that the first finding in the region where a bursa is about to develop is a myxomatous change of the connective tissue. Adventitious bursas are not present at birth. Trauma undoubtedly plays a major role in their formation. Unlike earlier writers, we do not believe that bacterial inflammation is the primary cause for the development of the adventitious bursas, in spite of the fact that collections of lymphocytes and polymorphonuclear leukocytes are found around the affected region. Degeneration is probably the factor which brings out these so-called inflammatory cells. What frequently is described by the surgeon as a bursa is myxomatous mucoid degeneration and cystic formation in connective tissue. Frequently there is more than one focus of myxomatous degeneration. These foci progressively grow larger and eventually coalesce.

The material present in the cavity of an adventitious bursa is of an indeterminate mucoid nature. It is the same material which was referred to by Langemak as fibrinoid. In its staining qualities and character it differs from mucus formed by epithelium. Its formation is a degenerative rather than a secretory process occurring in benign or malignant mesodermal tissues. Exactly what it represents is an enigma. In contrast to an adventitious bursa, a real bursa has an endothelial lining and does not exhibit any myxomatous change. Probably most of the true bursas are connected with joint cavities.

SUMMARY AND CONCLUSIONS

Adventitious bursas develop in fibrous connective tissue. They are not present at birth but are acquired. The process is one of mucoid or myxomatous degeneration of connective tissue. It appears to be degenerative rather than secretory. Repeated trauma to soft tissue over a bony prominence seems to be the causative factor. Adventitious bursas have no true lining, while true bursas have an endothelial lining.

EFFECT OF SULFATHIAZOLE ADMINISTERED ORALLY AND SULFANILAMIDE IMPLANTED LOCALLY ON CONTAMINATED WOUNDS

EXPERIMENTAL STUDY

JERE W. LORD JR., M.D.

ARTHUR H. BLAKEMORE, M.D.

AND

PAUL L. STEFKO

NEW YORK

During a study [1] of the nonsuture method of bridging a gap in the severed femoral artery of the dog, data were accumulated concerning the value of sulfanilamide implanted locally into the wound and also concerning the usefulness of sulfathiazole administered orally. Although the number of the experiments in which analysis of the data has been made is not large, the extensive nature of the experimental procedure plus the controlled condition of the operations make it worth while to report the results.

METHOD

After some 80 preliminary operations an exact technic was adopted, and with the time relations standardized a series of 30 carefully controlled operations were performed. In 20 animals the following procedure was followed: The right femoral artery was exposed under unsterile conditions, the incision being exactly 10 cm. in length. The artery was isolated for 2 cm. and divided between transfixion ligatures. All bleeders were clamped and tied with fine silk ties. Twenty-four hours later the animal was again anesthetized, intravenously administered pentobarbital sodium being the anesthetic agent, and after preliminary irrigation of the femoral wound on the right side with saline solution a 10 to 12 cm. segment of the left femoral vein was removed under aseptic conditions. The vein was set aside, care being taken to keep it sterile, and the femoral wound on the right side was excised completely, the operation including débridement of the ends of the artery. All bleeders were tied with arterial (B-1 Deknatel) silk. The wound was then irrigated with 250 cc. of saline solution and redraped. The two tube nonsuture technic was then carried out, vitallium tubes 3 mm. in outside diameter being inserted into the segment of the left femoral vein (fig. 1). The wound was closed carefully with interrupted sutures of arterial silk to the deep fascia and muscle and to the superficial fascia. The skin was not sutured, but the cut edges usually fell together as a result of the careful approximation of the superficial fascia. A collodion gauze dressing was applied. Postoperatively the wound was examined daily and the nature of the healing observed, as well as the pulsation of the venous segment and the distal artery. At the end of seven days all of the wounds were opened and the anastomoses examined to determine blood flow. The condition of the wound was carefully noted and the anastomosis resected and examined grossly for thrombosis.

With 10 animals exactly the same procedure was carried out as with the aforementioned group except for the substitution of the Carrel suture technic for the anastomosis of the

From the Departments of Surgery, Presbyterian Hospital, Columbia University, College of Physicians and Surgeons and the New York Hospital, Cornell University Medical College.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Cornell University Medical College.

1. Blakemore, A. H.; Lord, J. W., Jr., and Stefko, P. L.: The Severed Primary Artery in the War Wounded, Surgery **12**:488-508 (Sept.) 1942; Restoration of Blood Flow in Damaged Arteries: Further Studies on a Nonsuture Method of Blood Vessel Anastomosis, Ann. Surg. **117**:481-497 (April) 1943.

segment of vein to the cut ends of the right femoral artery. A second variation was that the wounds were studied for fourteen days instead of seven, because it had been observed in earlier series that with the Carrel method secondary hemorrhage or thrombosis might occur during the second week. With the nonsuture method failure, if it is going to occur, does so during the first seven days.

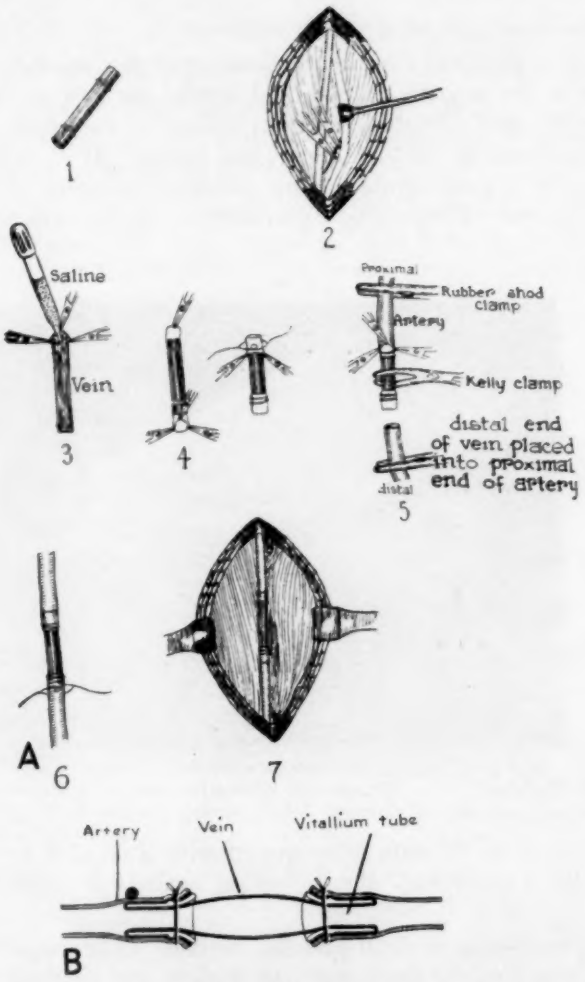

Fig. 1.—*A*, the various steps in the operation as carried out in the femoral artery: *1* shows the vitallium tube with its two ridges (sometimes grooves). *2* shows the artery and vein exposed. The vein is retracted and clamps have been placed upon a branch. We now think it is perhaps better technic to ligate the branch first, clamp distally and cut between. In *3*, the segment of vein on removal is irrigated with saline solution through a blunt-nosed eye dropper. In *4*, the vein has been pushed through the inside of the vitallium tube; the two ends are everted over the ends of the tube and are held in place with one or two ligatures of fine silk. In *5*, the distal end of the segment of vein is inserted into the proximal end of the artery and held there by two ligatures of fine silk; all ligatures are placed behind the ridges. In *6*, the snug ligature near the end of the vitallium tube, for the apposition of the artery and vein, is being tied. *7* represents the completed operation, showing the bridging of a gap of 2 cm. in the femoral artery. Two tubes were used instead of a single one in all instances.

B, the vein is brought through each vitallium tube and the everted ends held in place by ligatures. The ends of the divided artery are brought over the vitallium tube and held in place by ligatures; this method makes it possible to bridge a gap of any length, the limiting factor being the length of the venous transplant.

Into alternate wounds of all 30 dogs 1.5 Gm. of powdered sulfanilamide was sprinkled at the time of the arterial anastomosis. To 10 of the 20 dogs for which the two tube technic was used 1 Gm. of sulfathiazole was administered orally twice daily (9 a. m. and 5 p. m.). To all 10 of the dogs for which the suture technic was used 1 Gm. of sulfathiazole was administered similarly. Therapy with sulfathiazole was begun at the time of the unsterile division of the femoral artery.

RESULTS

There are two yardsticks for the evaluation of the results: (1) the character of the healing of the wounds as observed during the one or two week follow-up and at exploration and (2) the success or failure of the anastomoses to transport blood when examined at the end of the test period. It is worth noting that the latter criterion is a considerably more sensitive measure of minimal bacterial activity than the first. Cultures of material from the wounds were taken to check the above observations.

Fig. 2.—A perfectly healed (4+) wound one week after the performance of the anastomosis.

In order to express the data in as quantitative a fashion as possible under the conditions of the experiment, the following scale was used for evaluation of the wounds:

Grade 4 + implies a perfectly healed wound. The edges of the cutaneous incision are firmly joined; the fascia and muscle are relatively dry, are as pale as intact tissue in the same region of the dog and are healing firmly; the anastomosis is well enveloped by cleanly healing tissue (fig. 2).

Grade 3 + implies the same condition as 4 + except that the fascial and muscle layers are slightly edematous and reddened but no free fluid is present.

Grade 2 + signifies that the edges of the cutaneous incision are still adherent but that there are one or more pockets of free nonpurulent fluid deep in the wound. The fascia and muscle are only partially healed.

Grade 1 + implies that the edges of the cutaneous incision are separated; the wound is open to the deep fascia and muscle and some deep collections of seropurulent fluid are present (fig. 3).

Grade O signifies that the wound is wide open without any evidence of healing; collections of frank pus are present. The anastomosis may or may not be anatomi-

cally intact. Our observations in the past indicate that in all such wounds thrombosis of the venous segment occurs.

In the 30 animals under discussion no "O" wounds were observed, but they were noted in earlier series when twenty-four hour wounds were treated without débridement.

The following classification of the states of the anastomoses is employed:

+ patent with good blood flow and without any evidence of thrombosis.
++ thrombosed completely without any blood flow.
+++ partially thrombosed but with demonstrable flow of blood through the anastomosis at exploration.

Table 1 shows a comparison of 5 dogs into which sulfanilamide was implanted locally with 5 dogs for which no drug was used. For none of the 10 animals had sulfathiazole been used. Each wound of the treated group healed at least 2 +;

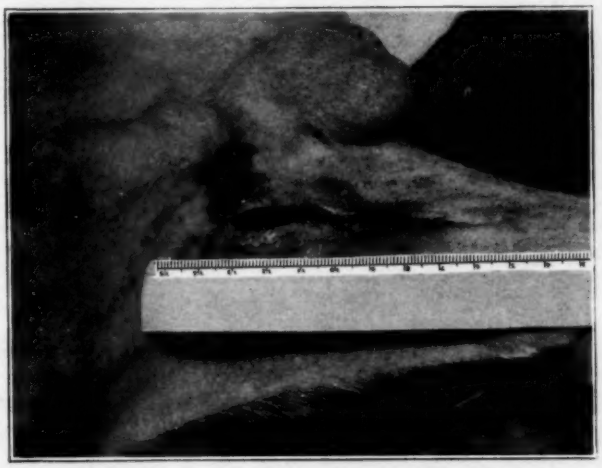

Fig. 3.—A wound which is healing poorly (1+) open to the deep fascia with some seropurulent fluid proximally.

TABLE 1.—*Effect of Local Implantation of Sulfanilamide into the Wound When Sulfathiazole Was Not Given Orally*

	Sulfanilamide		No Sulfathiazole	No Sulfanilamide	
	Wound	Anastomosis		Wound	Anastomosis
	3	++		1	++
	4	+		4	++
	4	++		2	+++
	2	++	*E*	2	++
	4	+		3	+
Total	17/20	2/5		12/20	1.5/5
Percentage of normal	85	40		60	30

E, one of the two series of 10 dogs in which nonsuture technic was used.
Wound: 4, perfectly healed; 3, well healed except for edema; 2, poor healing muscle and fascia—pockets of clear fluid; 1, edges of skin apart—open to deep fascia with seropurulent fluid; 0, no evidence of healing—frank pus present.

Anastomosis: +, patent, with good blood flow and without thrombosis; ++, thrombosed completely; +++, partial thrombosis but with some blood flow.

3 out of 5 had wounds graded 4, i. e., perfectly healed, and the average was 3.4 out of a possible 4. On the other hand, in the untreated group 1 dog had a 1 +

wound, only 1 out of 5 had a 4 + wound and the average was 2.4. In other words, healing was 25 per cent less successful than in the treated group.

Secondly, whereas only 1.5 of 5 untreated arterial anastomoses functioned, 2 of 5 of the treated ones were successful. (A partially functioning anastomosis is counted as half an anastomosis.) This difference, although small (10 per cent), is in the same direction as the state of the wounds of the two groups.

TABLE 2.—*Effect of Oral Sulfathiazole on the Wound and Anastomosis in Absence of Local Sulfanilamide*

Sulfathiazole			No Sulfanilamide		
	Wound	Anastomosis		Wound	Anastomosis
		A			
	4				
	4				
	4				
	1				
	4				
		D			*E*
	3	++		1	++
	4	+		4	++
	3	+++		2	+++
	4	+		2	++
	4	+		3	+
Total	35/40	3.5/5		12/20	1.5/5
Percentage of normal	88	70		60	30

A, series of 10 dogs in which Carrel suture technic was used. Only the 5 to which no sulfanilamide was given are shown. See table 3; *D*, one of the two series of 10 dogs in which nonsuture technic was used. Only the 5 to which no sulfanilamide was given are shown, was used. See table 3; *E*, one of the two series of 10 dogs in which nonsuture technic was used

TABLE 3.—*Effect of the Combination of Locally Implanted Sulfanilamide and Orally Administered Sulfathiazole on the Wound and Anastomosis* *

Sulfanilamide		Sulfathiazole	No Sulfanilamide	
Wound	Anastomosis		Wound	Anastomosis
4	+		4	+
4	+++		4	+++
3	++	*A*	4	+++
4	+		1	++
4	+		4	+++
4	+		3	++
4	+		4	+
4	+	*D*	3	+++
4	+		4	+
4	+		4	+
Total 39/40	8.5/10		35/40	6/10
Percentage of normal 98	85		88	60

* See tables 1 and 2 for explanation of above data.

Table 2 shows the efficacy of orally administered sulfathiazole in a group of animals none of which received sulfanilamide. Two groups of 5 dogs received 1 Gm. of sulfathiazole orally twice daily, and their wounds averaged 3.4 and 3.6 out of a possible 4. In contrast, the untreated group had an average of 2.4 out of a possible 4. In groups D and E, in which the nonsuture technic was used for all 10 animals, the difference in effective arterial anastomoses was 3.5 out of 5 (70 per cent) in the treated group as compared with 1.5 out of 5 (30 per cent) in the controls. It should be noted that in the sulfathiazole-treated group

3.5 (70 per cent) of the arterial anastomoses functioned, whereas in only 2 (40 per cent) of the group of sulfanilamide-treated dogs were the results satisfactory (table 1).

Table 3 reveals the interesting observation that the combined use of sulfanilamide locally in wounds and sulfathiazole orally brought about the best results of all, i. e., an average of 3.9 of a possible 4. The data in this table show that better results (10 per cent) are obtained in wound healing when one employs local implantation of sulfanilamide in addition to oral administration of sulfathiazole instead of relying solely on the latter. Moreover, 8.5 of 10 (85 per cent) of the arterial anastomoses in the combined treatment group functioned, in contrast to 6 of 10 (60 per cent) in the group for which only orally administered sulfathiazole was employed.

COMMENT

Although the data obtained in these experiments probably are not susceptible of careful statistical analysis, chiefly because of the limited number of experiments, the absolute trend of the findings, i. e., the character of healing the wounds and the patency of the arterial anastomoses, was always in favor of the animals treated with sulfonamide compounds. The interesting observation that there was no significant difference between the effect of sulfathiazole administered orally and that of sulfanilamide implanted locally on the healing of the wound proved that that criterion is not as sensitive as the determination of the patency of the anastomosis. When the latter method of study was used it was discovered that a 30 per cent difference existed in favor of sulfathiazole given by mouth. However, the combined treatment led to a further improvement of 10 per cent in the wound healing (to 98 per cent) and of 15 per cent in the success of the arterial anastomosis (to 85 per cent). It is worth noting that even for the animals given combined treatment, in which the degree of wound healing was 98 per cent, cultures gave positive results in all cases in which they were made (8 of 10) and the organism found was Staphylococcus aureus in 6 cases and Bacillus pyocyaneus and Bacillus proteus in 1 case each.

One possible explanation of the increased effectiveness of sulfathiazole orally over sulfanilamide locally, when the number of patent anastomoses is considered, is that the former drug was administered at the time of the initial unsterile ligation and division of the femoral artery, whereas the sulfanilamide was implanted locally at the time of the second operation, about twenty-four hours later. It is likely that the sulfathiazole would have been less effective if it had been withheld until the second operation. In any case the practical application of these observations to the wounded soldier would be the immediate administration, if possible, of sulfathiazole orally as soon as the injury had occurred and in addition the use of sulfanilamide locally after the wound had been débrided.

A highly significant observation which was made during these studies on delayed anastomoses of blood vessels has to do with the role of débridement in the treatment of wounds. In wounds twenty-four hours old, unless complete débridement was carried out, healing usually was poor (average 1 +) and in 13 of 13 cases complete thrombosis had occurred. In this series the 7 wounds into which sulfanilamide had been implanted average 1.5 +, in contrast to the 6 wounds without sulfanilamide, in which O healing was noted. In none of the foregoing series was sulfathiazole employed. The experimental data just mentioned confirm fully the experience of surgeons of World War I and of the present war that complete débridement is absolutely essential for the adequate healing of a war wound and that sulfonamide compounds locally and orally administered are merely

adjuncts to that treatment. The experimental data show further that the sulfonamide compounds in conjunction with careful débridement are of significant value, whereas when employed without excision of the contaminated and infected tissue they are only of slight aid as far as the wound is concerned.

CONCLUSIONS

During the study of the nonsuture method of bridging a gap in the severed femoral artery of the dog twenty-four hours after its unsterile ligation and division, the following conclusions were drawn concerning the value of sulfanilamide implanted locally and of sulfathiazole administered orally:

1. In the undébrided wound local implantation of sulfanilamide was of little value in regard to the healing of the wound and the patency of the arterial anastomoses.
2. In the carefully débrided wound sulfanilamide applied locally was of significant value in the healing of the wound and in the success of the anastomosis. Sulfathiazole administered orally was slightly more efficacious than sulfanilamide implanted locally.
3. The most satisfactory healing of wounds and the greatest number of successful anastomoses resulted from the combined use of sulfathiazole orally and sulfanilamide locally when careful débridement was done.

525 East Sixty-Eighth Street.

HEMANGIOMA OF THE SYNOVIAL MEMBRANE OF THE KNEE JOINT CURED BY SYNOVECTOMY

PAUL H. HARMON, M.D., PH.D.
SAYRE, PA.

The purpose of this report is to add a case of hemangioma of the knee joint to the few that have already been reported and to reemphasize the differential points and the care which must be observed in distinguishing this condition from hemophilic "arthritis" and other more common swellings of the knee joint.

It is probably safe to state that few hemangiomas of the knee joint are diagnosed immediately, even by experienced physicians. There are several reasons for this lack of accurate diagnoses, in spite of the fact that the clinical picture is rather characteristic, as will be seen later. The disease is rare, the symptoms are relatively nondisabling and nonprogressive and their occurrence is characteristically cyclic. No attempt will be made to review the literature, since Bennett and Cobey [1] have summarized the cases reported in the literature before 1939. At the time of their report 29 authentic cases, including 5 of their own, were on record in the surgical literature. In most of these cases symptoms had been present for years before the patient was seen by the physician who finally made the correct diagnosis. The patients had a history of recurring attacks of pain, swelling and limitation of motion. In no case was hemangioma noted in more than a single joint of each patient. The characteristic recurrent attacks marked by an elastic, doughy swelling which disappeared on elevation of the extremity were present in practically every case. In nearly all cases in which aspiration of the joint was carried out (7 of 8) bloody fluid was obtained.

REPORT OF A CASE

R. N., a boy aged 9 years, had been followed in the outpatient department of the Robert Packer Hospital and the Guthrie Clinic for eight months prior to his admission to the hospital because of a swelling of the left knee. The involved knee had never been particularly tender but had remained consistently swollen. For five years the patient had had intermittent bouts of slight to moderate pain associated with some swelling and a resultant diminution in motion. However, the knee had never been hot to touch, nor had there been any sinus formation. Prior to the patient's admission to the hospital, bloody fluid had been aspirated from the joint on two occasions. The results of several examinations of the blood, including an estimation of the number of platelets, were normal. The coagulation time averaged five minutes and the bleeding time one minute. The sedimentation rate was 10 mm. in sixty minutes.

Roentgen examination of the knee prior to operation (fig. 1) showed multiple small areas of subcortical absorption beneath the articular cortex of the tibia. These areas and the general appearance of the joint in the roentgenogram were suggestive of hemophilic changes. However, the condition of the blood and the fact that no other joints had ever been involved and that there had been no prolonged bleeding after trivial injuries all served to rule out hemophilia.

Inasmuch as the patient remained in good health without involvement of other joints but continued to be bothered by the swelling of the knee, it was thought advisable to perform an exploratory operation, since it was suspected that he might be suffering from a tumor of the synovial membrane.

From the Section on Orthopaedic and Traumatic Surgery, the Guthrie Clinic and the Robert Packer Hospital.

1. Bennett, G. E., and Cobey, M. C.: Hemangioma of Joints: Report of Five Cases, Arch. Surg. **38**:487-500 (March) 1939.

The left knee was opened through a 10 inch (25 cm.) lateral parapatellar incision on July 10, 1940, after a 1 inch (2.5 cm.) exploratory incision through the skin of the right thigh had confirmed the fact that the blood clotted normally. When the interior of the joint was exposed, the synovial membrane was found to be greatly hypertrophied, brick red and shaggy. About 60 to 100 cc. of serosanguineous fluid was present. As much of the synovial membrane as possible (estimated at 75 to 85 per cent) was then resected with the scissors. The joint was then closed in layers, the knee slightly but firmly compressed with two elastic bandages and the patient replaced in bed with traction of 7 pounds (3.2 Kg.) applied to the lower part of the leg by means of adhesive tape. The patient's subsequent course was uneventful, and he was discharged from the hospital on the twenty-sixth postoperative day. On discharge, the patient had about two thirds of the normal range of motion and the flexibility of the joint was increasing each day. Weight bearing was satisfactory and without pain.

Microscopic sections prepared from the shaggy, hypertrophied synovial membrane show many hemorrhages, large areas of macrophages packed with hemosiderin granules and universal distribution of small, thin-walled blood vessels (fig. 2).

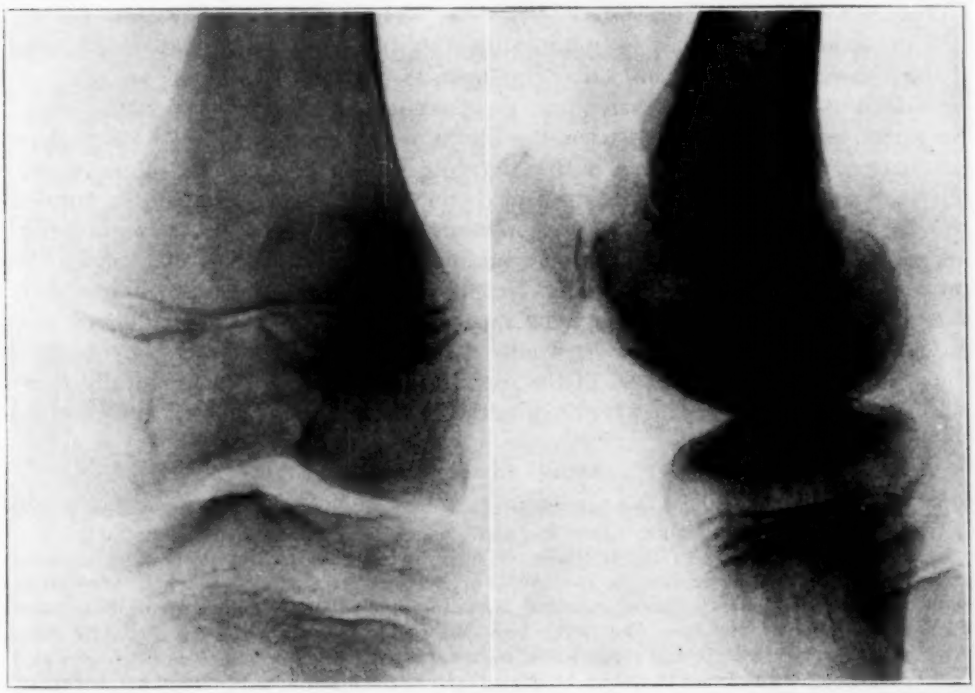

Fig. 1.—Preoperative roentgenograms of the knee which show multiple areas of subcortical demineralization. These roentgenograms are rather similar to those of patients with "hemophilic arthritis."

The patient has been followed for two and one-half years since the operation. There has never been any return of the swelling in the knee, and he has had no pain except that associated with passive and active motion before and immediately after discharge from the hospital.

DIAGNOSIS

All published reports of cases of hemangioma of the knee joint include the same striking symptoms and signs. The swelling of the joint is intermittent and usually of many years' duration, often dating back to early childhood. It is confined to a single joint and has never been of enough moment to detract from the patient's general health. Examination during an acute phase demonstrates that the swelling

disappears to a large extent on elevation or compression of the joint. Motion is limited by the swelling. Roentgenograms may show no abnormalities except the enlargement of the soft tissue shadow, or they may, as in my case, show subcondylar changes rather similar to those encountered after recurrent hemorrhages due to hemophilia. The final diagnosis is usually established at arthrotomy. If the operator opens the joint without interrupting the blood supply of the extremity with a constrictor, he is usually greeted by profuse hemorrhage, which, however,

Fig. 2.—Photomicrograph (× 125) of a section from the synovial and subsynovial tissue removed at operation. The synovial membrane is tremendously thickened, and there are many blood vessels in each synovial villus. The large, deeply stained subsynovial cells are macrophages loaded with hemosiderin. A large blood vessel at the extreme lower left has been sectioned. Elsewhere other blood vessels are seen filled with erythrocytes.

is not difficult to control by packing unless the tumor is one of the rare extensive hemangiomas which invade the adjacent muscle. Fortunately, in the case reported here observations of the joint in the ischemic state were possible. These will be described later.

PATHOLOGY

Two gross types of hemangioma are recognized—a diffuse form limited to the synovial membrane and an extensive cavernous form with invasion of the adjacent fascia and muscles. Except for the local extensions of the latter variation of the tumor, the tendency to spread in most cases is limited or nonexistent. In the case reported here, the changes were limited strictly to the synovial membrane and the subsynovial tissues, so that excision of the tumor was synonymous with excision of the synovial lining of the affected joint. The only reported case in which malignant change was observed was that of Downing and Mallory.[2]

The gross appearance of these tumors in the ischemic state is that of golden yellow, soft, friable synovial membrane. The color is strikingly apparent as soon as the joint is opened and is due to the extensive deposits of hemosiderin in phagocytic cells contained in the connective tissues between the interlacing network of the vessels (fig. 2). Villi are more or less abundant, and in some instances the interior of the joint assumes a shaggy appearance. The microscopic picture of large, irregular blood vessels contained in a stroma of loose connective tissue is identical in all cases. Numerous pigment-containing phagocytic cells are seen in the stroma. The size of the vascular area varies from tumor to tumor, being larger in the exceedingly vascular and invasive tumors and smaller in those restricted to the synovial tissues.

DIFFERENTIAL DIAGNOSIS

Differentiation of this condition is of extreme importance, from the point of view of both prognosis and treatment. A review of the literature and the experience gained from my case demonstrate that a permanent cure is often possible. Inasmuch as the final diagnosis is seldom made until the joint is opened, it would appear logical to excise the tumor, including synovial and subsynovial tissues, by the technic of synovectomy. Unless a constrictor is placed on the extremity above the joint after the diagnosis is confirmed by inspection at operation, or unless this precaution has been taken prior to opening the joint, accurate dissection is not possible because of the profuse hemorrhage. Hemophilic arthritis is definitely ruled out by the fact that the swelling has always been limited to a single joint and the history of subcutaneous hematomas and of bleeding from minor incised wounds is lacking. Finally, the surgeon will find that the patient with hemangioma has a normal number of blood platelets and a normal bleeding and clotting time, whereas in hemophilia the clotting time is greatly prolonged, especially during periods when patients are likely to come under medical observation owing to hemorrhages. It should be again emphasized here that no joint should be opened unless observations on the bleeding and clotting time have ruled out the presence of hemophilia.

The differentiation from chronic pyogenic infection of the knee joint and from tuberculosis of the knee should present few difficulties. The pain and swelling due to hemangioma are usually greater and the course of the disease more continuous. Pyogenic infections and tuberculosis produce characteristic alterations in the roentgenograms, and if no changes are observed in the osseous structures of the knee, aspiration of the joint must be relied on to add confirmatory data. Gross and microscopic observation of the aspirated fluid and cultures for bacteria will aid further in establishing the diagnosis. It should be remembered that the fluid is usually bloody when a hemangioma is present. Routine tuberculin and Wassermann tests may give a clue to tuberculous or syphilitic infections.

2. Downing, J. G., and Mallory, G. K.: Cavernous Hemangioma and Trauma: Report of a Case, Arch. Dermat. & Syph. **22**:414-422 (Sept.) 1930.

TREATMENT

Within certain limits, it would appear that the earlier in life surgical treatment is undertaken, the quicker will be the alleviation of the patient's symptoms and the establishment of a permanent cure. None of the sclerosing methods usually applied for hemangiomas elsewhere appears to be applicable to hemangioma of the knee joint. Excision by synovectomy appears to be the only satisfactory treatment for the diffuse tumors. However, Bennett and Cobey [1] reported 3 cures with roentgen rays and radium. While complete excision of the synovial membrane is technically impossible, enough of the tumor-bearing area can be removed in the routine synovectomy to effect a cure. Postoperative hemorrhage is never troublesome, since bleeding appears to be well controlled on closure of the joint. The prompt use of a constrictor on establishment of a diagnosis when the joint is opened is recommended, inasmuch as loss of life and/or loss of the extremity occasionally result from either profuse hemorrhage or attempts to control what appears to be a massive hemorrhage.

CONCLUSIONS

A characteristic case of diffuse synovial hemangioma of the knee is reported. Excision of the tumor-bearing synovial membrane was possible and effected a complete cure. The symptoms and signs of hemangioma, as well as the clinical and laboratory data, are characteristic enough so that a definite diagnosis should frequently be made prior to arthrotomy. Hemophilia, of course, should always be kept in mind and ruled out, since it is an absolute contraindication to arthrotomy.

SPONTANEOUS CLOSURE OF AN ARTERIOVENOUS FISTULA

REPORT OF A CASE

ROBERT F. BARBER, M.D.
BROOKLYN
AND
CAPTAIN JOHN L. MADDEN
MEDICAL CORPS, ARMY OF THE UNITED STATES

Although in earlier writings [1] it was stated that an arteriovenous aneurysm never heals spontaneously but on the contrary tends to increase in size, it is now a known fact that spontaneous closure of an arteriovenous communication may occur. This statement is supported both by experimental [2] and by clinical [3] evidence. As Holman [3b] stated: "Nature not infrequently eliminates it by thrombus and fibrous contraction around the abnormal opening." However, we are impressed with the paucity of material written on this particular phenomenon. For this reason we are submitting a detailed report of a case in which spontaneous closure of a femoral arteriovenous fistula occurred.

Reid and McGuire,[3a] referring to spontaneous closure of arteriovenous fistulas, stated: "In view of these experiences it is probably wise to use every effort to promote spontaneous healing before resorting to surgery." The same authors advised no immediate or early operation unless (1) hemorrhage, (2) diffuse hematoma or infection, (3) rapid cardiac damage and (4) rapidly rising venous pressure are present. He considered it more prudent to delay operation for three to six months after the occurrence of the fistula. There is a greater chance of spontaneous closure if the patient and the part are put at rest.

Holman [3c] opposed prolonged delay in operating: "If there is early evidence that the heart is increasing in size and that the blood pressure and pulse rate show marked variations on opening and closing a fistula, one may be certain that the lesion will not heal and must be eliminated by operation to avoid further effect upon the heart."

The advantages proclaimed by Reid and McGuire [3a] of delay in operation, provided that extenuating circumstances previously mentioned do not exist, are the following: (1) hemorrhage is absorbed; (2) tissues are restored to normal, which facilitates dissection of tissue and identification of structures; (3) danger of infection is lessened; (4) collateral circulation develops.

From the Department of Surgery, Long Island College Division, Kings County Hospital, Brooklyn.

1. Morel, P.: Des anévrismes artérioso-veineux du creux poplité, Thesis, Lyon, no. 61, 1899.

2. Reid, M. R., cited by Holman,[3b] p. 6. Vignola, cited by Holman,[5] p. 5.

3. (*a*) Reid, M. R., and McGuire, J.: Arteriovenous Aneurysms, Ann. Surg. **108**:643-693, 1938. (*b*) Holman, E.: Arteriovenous Aneurysm, New York, The Macmillan Company, 1937; (*c*) Recognition and Treatment of Arteriovenous Communications, Internat. Clin. **4**: 154-167, 1934. (*d*) Bird, C. E.: Spontaneous Closure of Arteriovenous Fistulas, Surgery **2**:924-929, 1937. (*e*) Reid, M. R.: Studies in Abnormal Arteriovenous Communications, Acquired and Congenital: I. Report of a Series of Cases, Arch. Surg. **10**:601-638 (March) 1925; II. The Origin and Nature of Arteriovenous Aneurysm, Cirsoid Aneurysms and Simple Angiomas, ibid. **10**:996-1009 (May) 1925; III. The Effects of Abnormal Arteriovenous Communications on the Heart, Blood Vessels and Other Structures, ibid. **11**:25-42 (July) 1925; IV. The Treatment of Abnormal Arteriovenous Communications, ibid. **11**:237-253 (Aug.) 1925.

For a complete discussion of the subject of arteriovenous aneurysm the reader is referred to the detailed studies of Reid [4] and Holman.[5]

REPORT OF CASE

W. D., a 24 year old Negro, was admitted to Kings County Hospital on Feb. 4, 1941, with a history of having been stabbed in the right groin with a paring knife at about 1 a. m. The blade of the knife broke off in the soft tissues of the thigh, and when it was withdrawn profuse bleeding occurred. He was brought to the hospital by ambulance and was in evident shock due to acute loss of blood. Bleeding was controlled with the aid of a pressure bandage, and shock therapy was instituted.

Physical examination revealed a well developed and well nourished Negro lying restlessly in bed and showing evidence of shock. The temperature was 98.6 F., the pulse rate 84 and the respiratory rate 18. The blood pressure was 70 systolic and 40 diastolic. The significant findings on examination were limited to the right lower extremity. Overlying the right femoral region 1.5 cm. below the middle and inner third of the inguinal ligament there was a stab wound approximately 5 mm. in length transverse to the long axis of the extremity. Below the wound was a hematoma measuring 5 cm. in its greatest diameter. Bleeding was acute and moderately profuse but was controlled by a pressure bandage. Further examination was deferred. A diagnosis of stab wound of the right thigh and shock due to acute loss of blood was made.

Detailed examination seven hours later revealed no evidence of active bleeding, increase in the size of the hematoma or undue tenseness of the surrounding soft tissues. Palpation of the area immediately about the wound revealed a pronounced thrill. On auscultation a loud systolic bruit was heard. The extremity distal to the fistula was warm, and the peripheral pulsations were full and equal to those of the opposite side.

The corrected diagnosis was stab wound of the right thigh and arteriovenous fistula between the right femoral artery and the right femoral vein.

Laboratory Data.—The urine was normal on repeated examination. On February 5 the red blood cell count was 4,100,000 and the hemoglobin content was 11 Gm. per hundred cubic centimeters (71 per cent). The white blood cell count was 10,450, with 52 per cent polymorphonuclear leukocytes, 46 per cent lymphocytes, 1 per cent eosinophil leukocytes and 1 per cent transitional cells. A second examination of the blood on March 4, 1941 revealed a red cell count of 3,580,000 and a hemoglobin content of 13 Gm. per hundred cubic centimeters (82 per cent); a white cell count of 11,500, with 68 per cent polymorphonuclear leukocytes and 32 per cent lymphocytes.

On February 7 the venous pressure in the right antecubital vein at heart level, with the fistula open, was 8 cm. of water. On February 17 it was 9.4 cm. of water, and on February 18, 9.4 cm. of water. An 18 gage needle was used.

On February 7 the pressure in the saphenous vein in the right ankle, with the patient in the horizontal position, was 14.6 cm. of water. The corresponding pressure on the left side was 15 cm. of water. A 20 gage needle was used.

On February 13 the circulation time, after injection of decholin into the left antecubital vein, was eighteen seconds, and on March 3 it was thirteen seconds.

The temperature of the skin (determined with the Taylor dermatherm) showed no abnormal variations.

Electrocardiograms made on March 3 and March 19 were normal. On February 5 roentgen examination of the soft tissues in the region of the stab wound revealed no evidence of any opaque foreign body. A teleoroentgenogram revealed a normal cardiac contour. The lungs were normal.

Course in the Hospital.—The patient responded satisfactorily to the usual measures to combat shock. Subsequent treatment was conservative, and the patient was kept in bed until the hematoma was completely absorbed and the wound had healed (twelve days).

Variations in the blood pressure after obliteration of the fistula by digital compression were demonstrated. Prior to closure blood pressure readings for the right arm were 150 systolic and 80 diastolic, and for the left arm, 150 and 80. After closure the readings were 155 and 110 and 160 and 110 respectively. Blood pressure readings in the lower extremities with the fistula open were 160 and 70 for the right leg and 168 and 90 for the left leg, with a demonstrable lowering of the diastolic pressure in the affected extremity.

Similarly, demonstrable differences in the pulse rate were recognized. With the fistula open the rate was 82 beats per minute. On closure of the fistula it dropped to 60.

4. Reid and McGuire.[3a] Reid.[3e]
5. Holman.[3b, e]

The patient's course in the hospital was uneventful, and he was discharged on March 25 to the outpatient department. He was readmitted on May 15 because of a minor infection of the right hand.

Examination at this time revealed the persistence of the previously described arteriovenous fistula in the right femoral region, with no alteration in the local lesion and no evident systemic abnormalities. Studies of blood volume on May 23 revealed a total blood volume of 5,275 cc. and a total plasma volume of 2,345 cc.; the percentage of erythrocytes was 55.4 and that of plasma 45.5. A teleoroentgenogram showed the cardiac contour to be within normal limits. There were no recent pathologic pleural or pulmonic changes present. The Wassermann reaction was negative.

He was discharged May 26 and returned August 6 for elective operation. Examination at this time revealed complete absence of the previously noted thrill and bruit.

COMMENT

The rapidity with which an arteriovenous communication can be produced and clinically recognized is adequately demonstrated in the case presented. The history of a stab wound in the region affected and the profuse but easily controlled bleeding were factors which suggested the possibilitiy of an arteriovenous fistula. The diagnosis was confirmed by the prompt development of a pronounced thrill and bruit which occurred within seven hours after the injury.

Twelve days after the patient's admission to the hospital the hematoma had been completely absorbed. The stab wound was well healed and there was no local tenderness. Despite normal physical activity he had no subjective complaints, and repeated studies failed to reveal any noticeable local or systemic changes as a result of the fistulous communication.

The relative difference in variation between the systolic and the diastolic blood pressure on closure of the fistula is noteworthy but readily explainable. The maintenance of an adequate peripheral resistance in conjunction with the elasticity of the vascular wall are the two basic factors for the development of the diastolic blood pressure. Changes in either of these factors will be productive of alterations in the diastolic pressure, which will be affected in direct proportion to the degree of change produced.

In the presence of an arteriovenous communication the reduction in peripheral resistance is the factor which is altered, with a resultant alteration in the diastolic pressure. The systolic pressure is affected, but to a lesser degree, so that a parallel variation in the systolic and diastolic pressures would not be expected to occur on closure of the fistula. However, cases have been reported [6] in which the immediate rise in the systolic pressure was as pronounced as that in the diastolic pressure after operative obliteration of the fistula. This rise is transitory and the pressure subsequently falls to a level which approaches or is equal to the preoperative systolic pressure. Conversely the diastolic pressure is stabilized at or falls only slightly below the level that obtained immediately after closure of the fistula.

The increase of 30 mm. of mercury in the diastolic pressure after the fistula was closed led us to believe that a fistulous communication of moderate size was present. Support was given to this belief when it was observed that there was an associated diminution in the pulse rate from 82 beats per minute to 60. These manifestations, associated with the pronounced thrill and bruit which persisted without evident alteration in intensity during an observation period of four months, appeared to indicate that a spontaneous closure would be unlikely. Therefore, surgical intervention was deemed advisable, but when the patient returned for operation at the completion of an arbitrary interval of six months, examination revealed that a spontaneous closure had resulted and that a cure had been effected.

6. Reid and McGuire.[3a] Holman.[3b]

Unless there are modifying circumstances, we favor the view expressed by Reid and McGuire,[3a] that an attempt at closure of the fistula by operation should be delayed for a period of six months. We further believe that if at the end of this time there is evidence of diminution in the size of the communication between artery and vein, as indicated by (1) diminution in intensity of the local thrill and bruit, (2) a distinct lessening of the variation in blood pressure and pulse rate on digital compression of the fistula and (3) absence of local or systemic alterations of function as indicated by clinical and laboratory studies (teleoroentgenograms, studies of blood volume, electrocardiograms, etc.), further observation is justifiable, provided that the patient can be kept under surveillance for a suitable period. If the foregoing signs of improvement have not appeared, or if a further period of observation is not feasible, operation should be performed.

1257 Dean Street.

ROLE OF THE CHEMICAL LABORATORY IN DIAGNOSIS OF NEOPLASTIC DISEASES OF BONE

HELEN QUINCY WOODARD, PH.D.
NEW YORK

Much confusion has existed regarding the significance of changes in the chemical composition of the blood and urine of patients with tumors of bone. This confusion arises mainly from the fact that the chemical changes are nonspecific, several diseases of unrelated cause being capable of causing the same chemical abnormality. If the mechanism of the chemical changes is understood, a consideration of the laboratory data will often establish a diagnosis which could not be made by clinical observation alone. It is the purpose of the present paper to consider the conditions under which this can be done. Only such chemical tests as can be made in the average well equipped hospital laboratory will be considered. For a few patients a diagnosis can be established only by means of the highly specialized procedures employed in metabolism wards, but these are outside the scope of the present paper. Non-neoplastic diseases of the bone will be discussed only so far as is necessary to distinguish between them and tumors of bone.

METABOLISM OF BONE

Before studying the disturbances associated with tumors of bone it is necessary to review the conditions which govern the metabolism of normal bone. These are represented diagrammatically in chart 1. Bones consist principally of tertiary calcium phosphate ($Ca_3[PO_4]_2$), but contain also dibasic calcium phosphate ($CaHPO_4$), calcium carbonate ($CaCO_3$) and calcium hydroxide ($Ca[OH]_2$). The proportions vary with the age and location of the bone, and hence are represented by the general formula $nCa_3(PO_4)_2.CaX$,[1] which is shown at the right of the diagram. The mineral constituents of bone are embedded in an organic matrix, and the structure contains blood vessels and encloses the marrow cavity. The latter elements are omitted from the diagram for the sake of simplicity, although they are subject to diseases which will be considered later. The constituents of bone are of course derived ultimately from food. Calcium and phosphorus are therefore represented in the column headed "Food" at the left of the diagram. Calcium carbonate is an essential constituent of bone, but, as carbonate deficiencies are unknown, this substance is not included in the diagram. While disease of bone due primarily to protein deficiency has been observed, it usually occurs secondarily to profound disturbances elsewhere in the body and will not be considered here. When the supplies of calcium or phosphorus in the food are inadequate, deficiency diseases of bone, such as rickets and osteomalacia, occur. The same diseases also develop when the diet is adequate but absorption is defective. This may occur in persistent diarrhea because of too rapid passage of the food through the digestive tract, or in sprue, probably owing to loss of calcium as insoluble calcium soaps. A more common cause of faulty absorption is deficiency of vitamin D. While the entire mechanism of the action of vitamin D is not yet known, it appears to be well established that the principal effect of the vitamin

From the Memorial Hospital for the Treatment of Cancer and Allied Diseases.

1. Huggins, C.: The Composition of Bone and the Function of the Bone Cell, Physiol. Rev. **17**:119-143 (March) 1937.

is to promote absorption of calcium.[2] Phosphorus is also lost in vitamin D deficiency owing to the formation of insoluble calcium phosphate with the unabsorbed calcium.

After calcium and phosphorus are absorbed from the digestive tract, they are transported in the blood stream to the tissues. In the course of normal or pathologic catabolism the tissues ultimately return these elements to the blood for excretion. The calcium content of erythrocytes is low.[3] The total calcium of the blood serum is made up of several fractions,[4] of which the most important are the ionized and the protein bound.[5] It is the ionized fraction of the serum calcium which has an important effect on the irritability of muscle. The level of ionized calcium in the serum is controlled by the parathyroids. Serum albumin is more effective than serum globulin in binding calcium.[6]

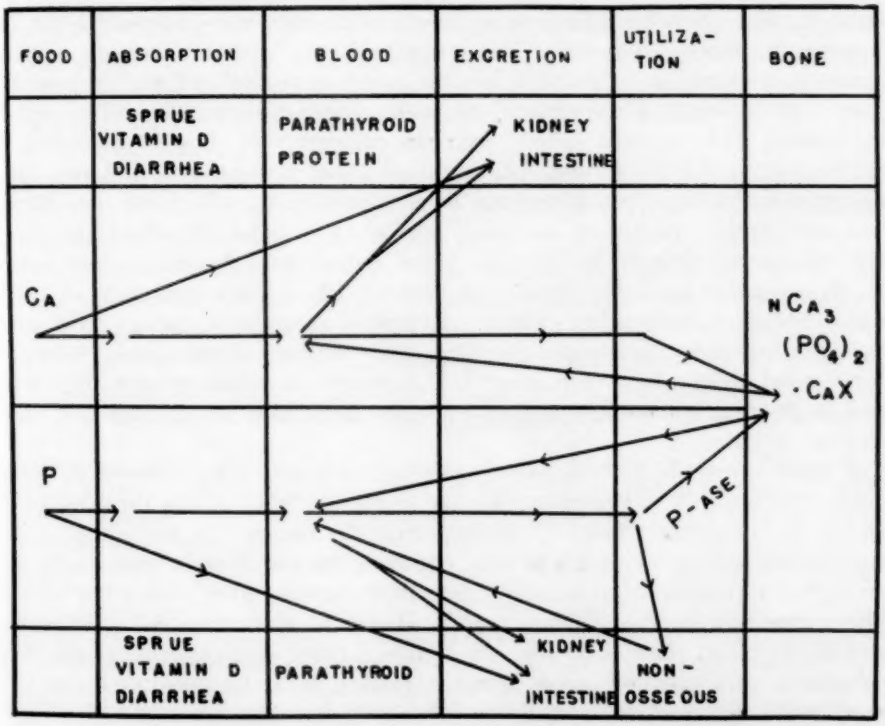

Chart 1.—Conditions which govern the metabolism of normal bone.

2. Nicolaysen, R.: Studies on the Mode of Action of Vitamin D: Influence of Vitamin D on Fecal Output of Endogenous Calcium and Phosphorus in Rat, Biochem. J. **31**: 107-121 (Jan.) 1937; Influence of Vitamin D on Absorption of Calcium and Phosphorus in Rat, ibid. **31**:122-129 (Jan.) 1937.

3. Larizza, P.: Sul contenuto in calcio dei globuli rossi del sangue umano, Biochem. e terap. sper. **22**:280-285 (June 30) 1935.

4. Benjamin, H. R., and Hess, A. F.: Forms of Calcium and Inorganic Phosphorus in Human and Animal Sera: Normal, Rachitic, Hypercalcemic, and Other Conditions, J. Biol. Chem. **100**:27-55 (March) 1933.

5. McLean, F. C., and Hastings, A. B.: Clinical Estimation and Significance of Calcium-Ion Concentration in Blood, Am. J. M. Sc. **189**:601-613 (May) 1935.

6. Gutman, A. B., and Gutman, E. B.: Relation of Serum Calcium to Serum Albumin and Globulins, J. Clin. Investigation **16**:903-919 (Nov.) 1937.

As the major portion of the calcium in the body is in the bones, osseous disease readily causes changes in blood calcium. In contrast to calcium, phosphorus is present in considerable amounts in all the tissues. It occurs in numerous organic compounds in the blood serum. The intermediate product in the transformation of these compounds is inorganic phosphate, and this is the ion which is usually determined in the study of disease of bones. Because this may be derived from nonosseous tissues as well as from bone, the concentration of inorganic phosphate in the serum is not a very sensitive indicator of changes in bone. In particular, ingestion of carbohydrate causes a marked temporary drop in serum inorganic phosphate.[7]

Calcium and phosphorus, whether recently absorbed from the food or derived from tissue catabolism, are carried by the blood to the excretory organs. Most of the calcium and phosphorus found in the feces have never been absorbed, but are residues of food. Small amounts of endogenous calcium and phosphorus do, however, enter the intestinal tract.[2] The intestine is not a true excretory organ, in the sense that excretion of calcium by this route is not related to the amount of calcium in the blood.[8] The principal excretory organ for calcium and phosphorus is the kidney. The normal kidney excretes calcium very slowly when the total serum calcium is 7.5 to 9.0 mg. per hundred cubic centimeters, and the rate of excretion rises rapidly when the serum level is greater than 11.5 mg. per hundred cubic centimeters.[9] It is not yet clear whether the renal threshold for calcium can be influenced directly by vitamin D or parathyroid hormone, but such an effect, if present, is probably small. In general, the urinary excretion of calcium parallels the blood level rather closely. Retention of calcium due to renal insufficiency does not occur unless the damage to the kidney is extremely severe. A primary renal defect has been described[10] which is characterized by inability to form ammonia, with compensatory excessive excretion of calcium and demineralization of bone.

The renal threshold for inorganic phosphate appears to be lowered by vitamin D, dihydrotachysterol and parathyroid, the relative effects of the three substances increasing in the order named.[11] In hyperparathyroidism the excretion of phosphorus by the kidney is so great that depletion of the bones results. In renal insufficiency, retention of inorganic phosphate occurs later than that of urea, but the serum inorganic phosphate usually begins to rise when the urea nitrogen content of the blood reaches 35 mg. per hundred cubic centimeters. If the hyperphosphatemia continues for some time, it results in a depression of the serum calcium, which in turn causes the bone disease known as renal rickets.

When adequate amounts of calcium and phosphorus reach the bone, they are deposited as complex calcium phosphates. The mechanism of mineralization has

7. Bodansky, A.; Hallman, L. F., and Bonoff, R.: Phosphatase Studies: VI. Non-Osseous Origins of Serum Phosphatase; Its Increase After Ingestion of Carbohydrates, J. Biol. Chem. **104**:473-482 (March) 1934.

8. McCance, R. A., and Widdowson, E. M.: Fate of Calcium and Magnesium After Intravenous Administration to Normal Persons, Biochem. J. **33**:523-529 (April) 1939. Adolph, W. H., and Liang, C. C.: Calcium in the Alimentary Tract of the Rat, J. Biol. Chem. **137**:517-523 (Feb.) 1941.

9. Albright, F.: Note on the Management of Hypoparathyroidism with Dihydrotachysterol, J. A. M. A. **112**:2592-2593 (June 24) 1939.

10. Albright, F.; Consolazio, W. V.; Coombs, F. S.; Sulkowitch, H. W., and Talbott, J. H.: Metabolic Studies and Therapy in Case of Nephrocalcinosis with Rickets and Dwarfism, Bull. Johns Hopkins Hosp. **66**:7-33 (Jan.) 1940.

11. Albright, F.; Sulkowitch, H. W., and Bloomberg, E.: Comparison of Effects of Vitamin D, Dihydrotachysterol (A. T. 10) and Parathyroid Extract on Disordered Metabolism of Rickets, J. Clin. Investigation **18**:165-169 (Jan.) 1939.

been the subject of investigations too extensive to be reviewed in detail here. It is well established, however, that calcifying cartilage can utilize calcium and phosphorus in inorganic solutions in vitro.[12] It is further well established that bone elaborates an enzyme, phosphatase, which splits organic phosphorus compounds to supply a local excess of inorganic phosphate.[13]

Bone phosphatase is known as an "alkaline phosphatase" because its activity is at a maximum in alkaline solution. It usually enters the circulation readily and may be demonstrated in the blood serum. While many nonosseous tissues contain alkaline phosphatase, nearly all the alkaline phosphatase in the blood serum is derived from the bones.[14] Alkaline phosphatase is excreted in the bile. The serum alkaline phosphatase is regularly elevated in obstructive jaundice and frequently elevated in hepatic insufficiency. Despite extensive study, it is not yet entirely clear whether this elevation of serum phosphatase is due to simple retention of bone phosphatase, or whether part of the excess phosphatase in the serum originates in the damaged liver. For diagnostic purposes, it is sufficient to remember that elevated values for alkaline phosphatase in the serum of jaundiced patients or of patients with enlarged livers cannot be considered as clearcut evidence of increased activity in the bone.

In subjects with normal livers the alkaline phosphatase of the serum usually parallels that of the bones rather closely. Evidence derived partly from examination of osseous tissue and partly from that of blood serum shows that the phosphatase activity of normal adult bone is low, while that of growing bone is much higher.[15] There is a compensatory increase in alkaline phosphatase when normal bone growth or repair is prevented owing to inadequate supplies of calcium or phosphorus, as in rickets or hyperparathyroidism.[16] Alkaline phosphatase is increased when normal new bone is being formed, as in fractures,[17] or when abnormal new bone is being formed, as in osteitis deformans, osteogenic sarcoma or osteoplastic metastatic

12. Shelling, D. H.; Kramer, B., and Orent, E. R.: Studies upon Calcification in Vitro: Inorganic Factors Determining Calcification, J. Biol. Chem. **77**:157-169 (April) 1928.

13. Robison, R.: The Possible Significance of Hexosephosphoric Esters in Ossification, Biochem. J. **17**:286-293, 1923.

14. Armstrong, A. R., and Banting, F. G.: Site of Formation of Phosphatase of Serum, Canad. M. A. J. **33**:243-246 (Sept.) 1935.

15. (*a*) Franseen, C. C., and McLean, R.: The Phosphatase Activity of Tissues and Plasma in Tumors of Bone, Am. J. Cancer **24**:299-317 (June) 1935. (*b*) Woodard, H. Q.: Acid and Alkaline Glycerophosphatase in Tissue and Serum, Cancer Research **2**:497-508 (July) 1942. (*c*) Yamane, T.: The Phosphatase and Pyrophosphatase of Bones and Cartilage, Arb. a. d. dritten Abt. d. anat. Inst. d. kaiserl. Univ. Kyoto, 1931, pp. 49-61 and 84-99.

16. (*a*) Barnes, D. J., and Munks, B.: Serum Phosphatase, Calcium, and Phosphorus Values in Infancy, Proc. Soc. Exper. Biol. & Med. **44**:327-331 (June) 1940. (*b*) Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: III. Serum Phosphatase in Diseases of the Bone; Interpretation and Significance, Arch. Int. Med. **54**:88-110 (July) 1934; (*c*) Phosphatase Studies: V. Serum Phosphatase as a Criterion of Severity and Rate of Healing of Rickets, Am. J. Dis. Child. **48**:1268-1278 (Dec.) 1934. (*d*) Gutman, A. B.; Tyson, T. L., and Gutman, E. B.: Serum Calcium, Inorganic Phosphorus, and Phosphatase Activity in Hyperparathyroidism, Paget's Disease, Multiple Myeloma and Neoplastic Disease, Arch. Int. Med. **57**:379-413 (Feb.) 1936. (*e*) Kay, H. D.: Plasma Phosphatase: II. The Enzyme in Disease, Particularly in Bone Disease, J. Biol. Chem. **89**:249-266 (Nov.) 1930.

17. Smith, J., and Maizels, M.: The Plasma Phosphatase in Rickets and Scurvy, Arch. Dis. Childhood **7**:149-158 (June) 1932. Botterell, E. H., and King, E. J.: Phosphatase in Fractures, Lancet **1**:1267-1270 (June 1) 1935. Hunsberger, A., and Ferguson, L. K.: Variations in Phosphatase and in Inorganic Phosphorus in Serum During Fracture Repair, Arch. Surg. **24**:1052-1060 (June) 1932. Kamada, K.: On Callus-Phosphatase and Its Participation in Healing Process of Fractures, Fukuoka-Ikwadaigaku-Zasshi **25**:5-6 (Feb.) 1932. Wilkins, W. E., and Regen, E. M.: Course of Phosphatase Activity in Healing of Fractured Bone. Proc. Soc. Exper. Biol. & Med. **32**:1373-1376 (May) 1935.

cancer.[18] Calcification in nonosseous tissues also may be associated with an increase in alkaline phosphatase.[19]

While not directly connected with bone metabolism, acid phosphatase is an enzyme whose determination is important in the diagnosis of disease of bone. Many tissues contain small amounts of phosphatases with a maximum activity at p_H 4 to p_H 5, but, so far as is known, the only tissue which contains extremely large amounts of this enzyme is the prostate gland.[20] Small amounts of acid phosphatase of unknown origin are present in normal blood serum, but as there is no difference in the serum values for normal males and females, it is evident that prostatic phosphatase does not enter the circulation of healthy men. The acid phosphatase from prostatic cancer which has not metastasized likewise does not enter the circulation. When cancer of the prostate metastasizes either to bone or to soft parts, excess amounts of acid phosphatase can usually, though not always, be demonstrated in the blood serum.[21]

LABORATORY METHODS

In interpreting laboratory data, it is necessary to know how large an experimental error is to be expected, and what conditions are likely to interfere with the validity of the determinations. Hence, a brief discussion of these points is desirable.

Serum Phosphatase.—The determination of phosphatase depends on the measurement of the amount of decomposition which is produced in a phosphate ester under standard conditions. Many methods have been described, but only two are in common use. One, using sodium beta glycerophosphate as a substrate, was developed by Bodansky [22] for alkaline phosphatase, and has been modified by Woodard [15b] for acid phosphatase. The other, using phenyl phosphate as substrate, was developed by King and Armstrong [23] for alkaline phosphatase and adapted for acid phosphatase by Gutman and Gutman.[24]

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18. Gutman, A. B., and Gutman, E. B.: Paget's Disease: Relative Constancy of Serum Phosphatase Levels Over Periods of Two Years, Proc. Soc. Exper. Biol. & Med. **33**:150-153 (Oct.) 1935. Woodard, H. Q.; Twombly, G. H., and Coley, B. L.: A Study of the Serum Phosphatase in Bone Diseases, J. Clin. Investigation **15**:193-201 (March) 1936. Woodard, H. Q., and Higinbotham, N. L.: The Correlation Between Serum Phosphatase and Roentgenographic Type in Bone Disease, Am. J. Cancer **31**:221-237 (Oct.) 1937. Franseen and McLean.[15a] Woodard.[15b] Bodansky and Jaffe.[16b] Gutman, Tyson and Gutman.[16d] Kay.[16e]

19. Regen, E. M., and Wilkins, W. E.: Phosphatase in Heterotopic Bone Formation Following Transplantation of Bladder Mucosa, J. Lab. & Clin. Med. **20**:250-252 (Dec.) 1934. Wilkins, W. E.; Regen, E. M., and Carpenter, G. K.: Phosphatase Studies on Biopsy Tissue in Progressive Myositis Ossificans, Am. J. Dis. Child. **49**:1219-1221 (May) 1935. Woodard.[15b]

20. Kutscher, W., and Wolbergs, H.: Prostataphosphatase, Ztschr. f. physiol. Chem. **236**: 237-240, 1935. Kutscher, W., and Wörner, A.: Prostataphosphatase: II, ibid. **239**:109-126, 1936. Gutman, A. B., and Gutman, E. B.: "Acid" Phosphatase and Functional Activity of the Prostate (Man) and Preputial Glands (Rat), Proc. Soc. Exper. Biol. & Med. **39**:529-532 (Dec.) 1938.

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22. Bodansky, A.: Phosphatase Studies: II. Determination of Serum Phosphatase; Factors Influencing the Accuracy of the Determination, J. Biol. Chem. **101**:93-104 (June) 1933.

23. King, E. J., and Armstrong, A. R.: A Convenient Method for Determining Serum and Bile Phosphatase Activity, Canad. M. A. J. **31**:376-381 (Oct.) 1934.

24. Gutman, E. B., and Gutman, A. B.: Estimation of "Acid" Phosphatase Activity of Blood Serum, J. Biol. Chem. **136**:201-209 (Oct.) 1940.

Determinations of phosphatase are difficult and tedious and require the services of a well trained technician. An error of ± 5 per cent is to be expected under ordinary conditions, and a somewhat larger one when very high values are encountered unexpectedly. Systemic errors as large as 50 per cent may be made when the p_H is not adequately controlled in the determination of alkaline phosphatase. For acid phosphatase some variation in p_H is permissible. For alkaline phosphatase serum may be kept overnight in the ice box, but for acid phosphatase it is essential that the determination be made as promptly as possible.[25] Normal values for alkaline phosphatase in adults are 1.5 to 5.0 Bodansky units or 5.0 to 17.5 King-Armstrong units per hundred cubic centimeters of serum. For children the normal value for serum alkaline phosphatase ranges from the upper adult normal value to three times this amount, depending on the rate of growth. Normal values for acid phosphatase in adults are 0 to 1.0 Bodansky units or 0.6 to 3.0 King-Armstrong units per hundred cubic centimeters of serum. Little work has been done on acid phosphatase in children.

Serum Inorganic Phosphate.—The most satisfactory method for determination of serum inorganic phosphate is that described as a part of Bodansky's procedure for phosphatase. No special technical difficulties are ordinarily experienced. Results are commonly reported as milligrams of phosphorus (not phosphate) per hundred cubic centimeters of serum. Normal fasting values for adults are usually between 2.5 and 4.0 mg. per hundred cubic centimeters, although readings as high as 4.5 mg. are found occasionally. The amount of inorganic phosphorus in normal children ranges between 4.0 and 6.0 mg. per hundred cubic centimeters, and may be even higher in infants.[16a] The amount of inorganic phosphorus in the serum is lowered by the ingestion of carbohydrates.

Total Serum Calcium.—The total calcium of the serum is usually determined by methods based on that of Kramer and Tisdall.[26] The method is simple and easy and is usually accurate to 1 per cent. It has the disadvantage that it is possible, through loss of precipitate or inadequate washing of precipitate, to make gross errors without altering the appearance of the material sufficiently to give warning that the results are invalid. For this reason determinations should be done in duplicate whenever possible and should be repeated in critical cases.

Normal values for total serum calcium in the adult have been reported as ranging from 9.0 to 12.0 mg. per hundred cubic centimeters. This wide range may be due in part to the experimental errors mentioned above. In my experience, the great majority of normal adults have serum calcium values between 10.0 and 11.0 mg. per hundred cubic centimeters. Values between 11.0 and 12.0 are occasionally seen in healthy persons who have been exposed to the sun or who have been taking vitamin D. A transitory rise may occur in emotional disturbances accompanied by hyperventilation.[27] It is my opinion that, in an adult, a serum calcium lower than 10.0 mg. per hundred cubic centimeters indicates suboptimal nutrition. The total serum calcium of infants and children averages about 1 mg. per hundred cubic centimeters higher than that of adults.

Total Serum Protein.—Numerous methods for the determination of serum protein depending on the decomposition of the protein and the measurement of the resulting ammonia are in common use in clinical laboratories. These methods are usually reliable but time consuming and expensive. A method based on the deter-

25. Woodard, H. Q.: Unpublished data.

26. Kramer, B., and Tisdall, F. F.: A Simple Technique for the Determination of Calcium and Magnesium in Small Amounts of Serum, J. Biol. Chem. **47**:475-481 (Aug.) 1921.

27. Albright, F.: Personal communication to the author.

mination of the specific gravity of the serum [28] has recently come into favor. The method is quick, and is entirely satisfactory, except in serums containing abnormally large amounts of cholesterol. Determinations of albumin-globulin ratio are seldom necessary in the diagnosis of tumors of bone. Normal values for total serum protein usually lie between 6.3 and 8.0 Gm. per hundred cubic centimeters, although slightly lower or higher values are sometimes found.

Various other blood tests, such as those for urea nitrogen and bilirubin, are often necessary to establish the presence or absence of systemic disease which may affect the bones, but the methods for most of these tests are too well established to require comment here.

The only tests of urine which are commonly employed in the diagnosis of tumors of bone are those for Bence Jones protein and for calcium.

The test for Bence Jones protein is a qualitative one, and the result may be obscured by other urinary proteins. Negative findings are not significant, not only for this reason but because many patients with plasma cell myeloma excrete this protein only intermittently or not at all.

Most methods for measuring calcium in the urine depend on precipitation as the oxalate with subsequent titration or ignition and weighing. For accurate balance studies the more tedious gravimetric methods probably are necessary. For such problems as, for instance, distinguishing between nutritional osteoporosis and hyperparathyroidism, the titrimetric method of Shohl and Pedley [29] is satisfactory, provided that care is taken to control the alkalinity of the precipitation mixture and to wash the precipitate thoroughly. In many cases in which it is necessary only to establish the order of magnitude of calcium excretion, it is sufficient to test the urine by means of the Sulkowitch reagent.[30] This is a semiquantitative test which may be used in following the effect of therapy in cases of parathyroid disturbances in much the same way that the Benedict qualitative test is used in cases of diabetes.[9]

DIFFERENTIAL DIAGNOSIS

While some types of disease of bone may develop in patients of any age, others are much more common in the earlier or in the later years of life. Hence it is convenient to consider first the conditions most often seen in children and young adults, and then to group together those more frequent in middle-aged and elderly patients. The first group includes benign local overgrowths, solitary bone cysts, giant cell tumors, osteogenic sarcoma, endothelioma of bone and reticulum cell sarcoma of bone; the second includes metastatic cancer in bone and plasma cell myeloma. In each group the non-neoplastic diseases most likely to be confused with tumors will also be discussed.

Primary Tumors of Bone.—The majority of primary tumors of bone occur in children or young adults. Hence, in interpreting the chemical findings it is necessary to remember that the value for serum calcium of children is slightly, and that of serum inorganic phosphorus definitely, above the adult normal. The amount of alkaline phosphatase in the serum varies with the rate of growth. A sick child who has stopped growing temporarily may have a value for serum alkaline phos-

28. Weech, A. A.; Reeves, E. B., and Goettsch, E.: The Relationship Between Specific Gravity and Protein Content in Plasma, Serum and Transudate from Dogs, J. Biol. Chem. **113**:167-174 (Feb.) 1936.

29. Shohl, A. T., and Pedley, F. G.: A Rapid and Accurate Method for Calcium in Urine, J. Biol. Chem. **50**:537-544 (Feb.) 1922.

30. Barney, J. D., and Sulkowitch, H. W.: Progress in the Management of Urinary Calculi, J. Urol. **37**:746-762 (June) 1937.

phatase within the normal limits for an adult, while an adolescent boy may have three times this amount. The alkaline phosphatase usually reaches the normal adult level about the time the femoral epiphyses close. In these young patients, disease of the liver is uncommon and seldom needs to be considered in interpreting the phosphatase findings.

In the numerous abnormalities, such as chondroma, osteochondroma, osteoma and exostosis, which are characterized by benign localized overgrowth of bony elements, the abnormal tissue contains about the same amount of alkaline phosphatase as normal bone. There are no changes in the amounts of calcium, phosphorus or phosphatase in the serum. If an elevated alkaline phosphatase is encountered in these conditions, the suspicion is warranted that the local process is undergoing malignant change or that disease of bone is present elsewhere in the body.

Bone Cyst.—The type of solitary bone cyst which occurs in the long bones of children causes no change in the chemical composition of the blood. The normal values for calcium and phosphorus and the absence of significant elevation in alkaline phosphatase distinguish these cysts from those caused by hyperparathyroidism.

Giant Cell Tumor.—The material obtained on curettage of benign giant cell tumors usually contains negligible amounts of alkaline phosphatase, and there is no evidence that the bone adjacent to the tumor produces an excess of this enzyme except, perhaps, when fracture has occurred. In tissue from a malignant giant cell tumor there may or may not be considerable amounts of alkaline phosphatase. The value for alkaline serum phosphatase of patients with benign giant cell tumors is usually in the upper normal range; values for serum calcium and phosphorus are normal. In my experience, whenever the value for serum alkaline phosphatase of patients with giant cell tumors has been definitely above normal (6 to 9 Bodansky units) the tumors showed aggressive tendencies or were frankly malignant. The presence of normal amounts of alkaline phosphatase in the serum does not prove that the tumor is benign.

Osteogenic Sarcoma.—Tissue from an osteogenic sarcoma may contain alkaline phosphatase in amounts ranging from those in normal bone (0.1 to 0.5 Bodansky units per gram) to over 100 units per Gm. Two to 10 units is the common range. There is no definite correlation between phosphatase activity and histologic type, although the activity of medullary tumors averages somewhat lower than that of the cortical ones. In general, the greater the formation of new bone, the greater the phosphatase activity, but there are some extremely malignant tumors which contain abundant phosphatase but lay down little new bone. If osteogenic sarcoma is treated by external roentgen irradiation, and if the dose to the tumor (not the skin) equals or exceeds 4,000 r, the phosphatase-producing mechanism is nearly always completely inactivated. Smaller doses result in irregular or incomplete inactivation. Resumption of tumor growth is accompanied by resumption of the production of phosphatase.

The alkaline phosphatase in tissue from an osteogenic sarcoma usually enters the circulation readily and can be measured in the serum. The value may be 10, 20 or even 50 units in excess of the normal for the patient's age. There are, however, some sclerosing osteogenic sarcomas which contain abundant phosphatase but which cause little elevation in the serum readings. Such tumors have a prognosis better than the average. On the other hand, a large amount of alkaline phosphatase in the serum always indicates that the tumor is rather active. If such a tumor has

failed to lay down new bone, the prognosis is especially bad. The values for calcium and phosphorus in the serum of patients with osteogenic sarcoma are normal.

When a patient with osteogenic sarcoma has a high concentration of serum alkaline phosphatase, and the tumor is removed by operation or inactivated by irradiation, the serum phosphatase content falls to normal. Normal levels are reached within two weeks after amputation. If the value for phosphatase does not drop to normal, then residual active disease is present. If the value for the serum alkaline phosphatase of a patient falls to normal and later begins to rise again, metastases are probably developing or an irradiated primary tumor is becoming reactivated. The absence of a rise does not preclude the presence of metastases, since some metastatic deposits, although producing phosphatase, do not allow the enzyme to enter the circulation.

Endothelioma of Bone; Ewing's Tumor.—As this is a tumor of the endothelial, rather than the osseous, elements of bone, the tumor tissue itself does not produce significant amounts of alkaline phosphatase. There is usually a certain amount of reaction in the bone surrounding the tumor, with production of moderately increased amounts of phosphatase. This may lead to an increase in the value for alkaline phosphatase in the serum of 1 to 3 units per hundred cubic centimeters. Such small elevations can be detected with fair certainty in adults, but in children they are masked by the great variability of the normal values. For adults with Ewing's tumor, the values for serum alkaline phosphatase may be used in studying the effect of treatment in exactly the same way that they are for patients with osteogenic sarcoma. The results of such follow-up studies on children are too indefinite to be worth subjecting the young patients to venipuncture. Ewing's tumor causes no changes in the values for serum calcium and phosphorus.

Reticulum Cell Sarcoma of Bone.—In patients with this disease the concentrations of serum calcium and phosphorus are normal and the amount of serum alkaline phosphatase may or may not be slightly elevated. Thus, chemical studies are of no help in distinguishing this tumor from endothelioma or inflammatory disease of bone, both of which it often resembles.

Rickets.—A young patient with a tumor of bone may also have rickets. The high values for serum alkaline phosphatase caused by the latter disease should not be confused with those due to osteogenic sarcoma. In osteogenic sarcoma the values for serum calcium and phosphorus are normal, while in rickets, one or both are low.

Inflammatory Disease of Bone.—This is often confused with various neoplasms of bone and requires separate study. No conspicuous changes in the amounts of serum calcium and phosphorus are found in inflammations of bone. Except in syphilitic disease the serum alkaline phosphatase is either normal or very slightly elevated. The type of productive osteitis which sometimes resembles periosteal osteogenic sarcoma seldom causes any elevation in the amount of serum phosphatase. In such doubtful cases a diagnosis of osteogenic sarcoma is more probable the higher the value for phosphatase, although a normal value does not exclude osteogenic sarcoma. Osteolytic neoplastic diseases of bone cannot be distinguished from destructive nonsyphilitic infections of bone by study of the chemical composition of the blood. In my experience, syphilitic disease of bone is usually associated with a rather high value for serum alkaline phosphatase. It is not known whether this is due to excessive production of alkaline phosphatase by the bone or to inadequate excretion of phosphatase by a damaged liver. The combination of an osteolytic lesion, a positive serologic reaction for syphilis and a value for serum

alkaline phosphatase of 10 to 20 Bodansky units per hundred cubic centimeters makes it extremely probable that the lesion is syphilitic.

Metastatic Cancer in Bone.—When cancer originating in soft tissue metastasizes to bone, the bone may or may not attempt to repair the damage. When little or no attempt at repair is made, little alkaline phosphatase is produced by the bone, and the lesion is predominantly destructive. When an attempt at repair is made, abundant alkaline phosphatase is produced, and the lesion is osteoplastic. The alkaline phosphatase produced by bones which are the site of carcinoma metastases apparently enters the circulation readily, so that there is usually a close correlation between the degree of osteoplasia of the lesion, the amount of alkaline phosphatase found in extracts of the affected bone and the amount of alkaline phosphatase in the serum.

The majority of all metastases to bone are osteolytic, those originating in cancers of the breast, thyroid and kidney being perhaps the most conspicuous. Metastases from cancer of the prostate are almost the only ones which elicit excessive production of alkaline phosphatase and new bone formation with great regularity. In a series of cases from the Memorial Hospital, about 80 per cent of patients with metastases to bone originating in cancers of organs other than the prostate had predominantly osteolytic metastases. In contrast to this, 75 per cent of the metastases to bone from carcinoma of the prostate were almost wholly osteoplastic, and nearly all the remainder showed some degree of formation of new bone. No satisfactory explanation has ever been advanced as to why the bones should differ so much in their response to invasion by different types of cancer. The difference is probably a quantitative rather than a qualitative one, since all gradations in degree of new bone formation are sometimes seen in different bones in the same patient, and since, especially in prostatic carcinoma, individual metastatic areas tend to become more osteoplastic with the passage of time.

With the sole exception of metastatic cancer of the prostate, the site of origin of cancer metastatic to bone cannot be determined by chemical means. Despite this, chemical examination of the blood and urine often gives valuable information as to the existence, extent and activity of metastases to bone.

The typical patient with osteolytic metastases to bone has a slightly elevated value for serum alkaline phosphatase, readings being perhaps 6 to 7 Bodansky units per hundred cubic centimeters. The values for serum calcium and phosphorus tend to be at the upper normal limits or a little above, values in the neighborhood of 12.5 and 4.5 mg. per hundred cubic centimeters respectively being common. The urinary calcium excretion is high even when the patient is on a calcium-poor diet. Even with osteolytic disease the value for serum alkaline phosphatase may rise as high as 20 units, and calcium and phosphorus values of 16.0 and 5.5 mg. respectively or even higher are sometimes seen. Elevations of values for calcium and phosphorus tend to occur together and are less frequent the greater the amount of alkaline phosphatase. It is probable that the elevation of serum calcium and phosphorus is due to a flooding of the circulation with the end products of destruction of bone. Under ordinary circumstances these are excreted by the kidney without significant alteration in the chemical composition of the blood, but when the rate of osteolysis becomes excessive the kidney can no longer keep pace with it, and accumulation in the blood results.

Increases in the amount of inorganic phosphorus and alkaline phosphatase in the serum do not in themselves cause clinical symptoms, although the lesions causing them usually do. Increases in serum calcium, from whatever cause, may be a serious clinical problem. A value of 13.0 mg. per hundred cubic centimeters or

above may cause nausea, lassitude and mental confusion. Such elevations may occur in patients with metastatic cancer in bone even when they are still in sufficiently good general condition to be ambulatory. An erroneous diagnosis of cerebral or gastrointestinal metastases may be made in such circumstances if the serum calcium is not studied.

Patients with osteoplastic metastatic cancer commonly have marked increases in serum alkaline phosphatase, values of 20 to 30 Bodansky units per hundred cubic centimeters being common, and values in excess of 100 units being obtained occasionally. In these patients the calcium and phosphorus of the serum are not increased, and, indeed, the amount of calcium averages somewhat below normal. The urinary excretion of calcium is within normal limits. In these metastases the large amounts of alkaline phosphatase produced by the damaged bone are sufficient to protect it from disintegration. The process is not capable of preserving normal bone structure, but it is able to preserve the constituents of the bone. There is therefore no flooding of the circulation with breakdown products, and the values for serum calcium and phosphorus do not rise.

In actual practice, patients are often encountered whose blood chemical findings present a picture intermediate between those of the two groups described, and some cases of known metastatic cancer to bone show no abnormalities in the chemical composition of the blood. A review of blood chemistry of 250 in our cases with known bone metastases shows that in about three fourths of them an increased amount of calcium, phosphorus or alkaline phosphatase was present. Therefore, although normal results of chemical examination of the blood give no assurance that metastases to bone are absent, they make the presence of such metastases somewhat improbable. An elevated value for serum alkaline phosphatase, on the other hand, nearly always means that disease of either the bones or the liver is present. As the values for alkaline phosphatase will not permit one to distinguish between disease of bone and metastatic or other disease of the liver, it is necessary, before accepting an elevated value for serum alkaline phosphatase as definite evidence that there are metastases to bone, to be sure that there are no signs of disease of the liver.

As has been previously explained, the prostate gland, whether normal, hypertrophied or cancerous, contains large amounts of acid phosphatase. So far as is known at present, this enters the circulation only when a cancerous prostate has ruptured its capsule. An increase in serum acid phosphatase is considered pathognomonic of metastasizing carcinoma of the prostate, and it may occur whether the metastases are to soft parts or to bone. The presence of a normal serum acid phosphatase does not exclude a diagnosis of metastasizing prostatic cancer. In the series from the Memorial Hospital of 61 patients with prostatic cancer with known metastases to bone, 69 per cent had elevations of the value for serum acid phosphatase when first seen; of 37 patients with prostatic cancer with evidence of extension to soft tissues but without known metastases to bone, 41 per cent had elevations. In the majority of cases in which initial readings were normal, the values rose later in the course of the disease. In a few patients, either because the tumor does not produce large quantities of acid phosphatase or because the enzyme does not enter the circulation, the amount of serum acid phosphatase never rises much above the normal limits. We have seen patients in a terminal stage of metastatic prostatic cancer whose serum acid phosphatase was only 2 to 5 Bodansky units per hundred cubic centimeters, and others with readings of 100 units or even, in 1 case, 300 units. For this reason a single determination of serum acid phosphatase does not give a reliable indication of the activity of the disease, but changes in the value for serum acid phosphatase in any one patient give a very sensitive

indication of his clinical progress. In particular, a prompt drop in the value for serum acid phosphatase after the institution of endocrine treatment shows that a favorable clinical response may be anticipated; the failure of the value to drop within one to two weeks shows that the patient is probably refractory to this type of treatment; and a rise in the amount of acid phosphatase in the serum of a patient who has previously shown a satisfactory drop indicates that a clinical relapse may be expected within one to two months.

The great majority of metastases to bone from carcinoma of the prostate show a significant degree of new bone formation. Patients with this condition exhibit an elevation in the value for serum alkaline phosphatase with great regularity, and do not differ in this respect from patients with osteoplastic metastases from cancers originating in other organs. It must be emphasized that in the serum of patients with carcinoma of the prostate metastatic to bone the acid phosphatase is produced by the cancer in the bone or in other regions, while the alkaline phosphatase is produced by the bone around the cancer. The two enzymes may, and frequently do, vary independently. Patients with metastases to bone from carcinoma of the prostate who are receiving endocrine therapy often show a rise in the amount of serum alkaline phosphatase during the first one to two months after the beginning of treatment, followed later by a drop to or toward normal levels. The presence or absence of this rise is not related to the clinical response. Its cause is obscure and cannot be discussed in detail here.

Plasma Cell Myeloma.—This condition, like endothelioma of bone, is a disease in bone but not of bone. Because it occurs in the later age groups and results in destruction of bone, it is often difficult to distinguish from metastatic disease. When active and uncomplicated, it resembles osteolytic metastatic disease in causing slight elevations in the amounts of alkaline phosphatase, phosphorus and calcium in the serum, the reason for these changes being the same in both conditions. The value for serum acid phosphatase tends to be in the upper normal range, but, in our experience, does not rise above normal limits. The distinguishing chemical change in plasma cell myeloma is in the protein constituents of blood and urine. It has been known for many years that about 60 per cent of patients with plasma cell myeloma excrete Bence Jones protein in the urine at some time during their illness. Recently Moore, Kabat and Gutman [31] have shown that in plasma cell myeloma there may be one or several of a group of abnormal constituents in the globulin fraction of the serum. These may or may not result in a marked increase in the total serum protein. In the average hospital laboratory it is not possible to make protein fractionations such as these, but it is possible and easy to determine total serum protein and urinary Bence Jones protein. If a patient with osteolytic bone disease has a positive test for Bence Jones protein in the urine, or a total serum protein of 8.5 Gm. per hundred cubic centimeters, or both, it is reasonably certain that he has plasma cell myeloma. Negative findings do not exclude this diagnosis. Similar changes are sometimes observed in hepatic disease, leukemia and lymphogranuloma venereum, but these can usually be distinguished clinically from plasma cell myeloma. Severe renal impairment is common in plasma cell myeloma, and the extremely high values for serum inorganic phosphorus sometimes found may be due to retention of phosphorus by the damaged kidney rather than to excessive osteolysis.

There are two types of non-neoplastic disturbances of bone that occur in elderly people, especially women, which may readily be confused with neoplastic disease

31. Moore, D. H.; Kabat, E. A., and Gutman, A. B.: Bence-Jones Proteinemia in Multiple Myeloma, J. Clin. Investigation **22**:67-75 (Jan.) 1943.

of bone. They are osteomalacia and senile osteoporosis. They are characterized by demineralization, which occurs in the entire skeleton but is most conspicuous in the spine, where it leads to collapse of vertebrae, pain, disability and deformity.

Osteomalacia in the adult is the analogue of rickets in the child and is caused by insufficient intake or faulty absorption of calcium, phosphorus or protein or all three. Patients with this disturbance, although they may be fat, always appear ill nourished. They are notoriously unreliable in their accounts of what they eat, but when a satisfactory history can be obtained, it will show either long-continued poor diet or chronic indigestion. In the serum, the amounts of calcium or phosphorus or protein or all three may be low, according to the nature of the deficiency. The changes are not marked, typical values for calcium being 9.0 to 9.5 mg., for phosphorus, 2.2 to 2.5 mg. and for protein, 5.8 to 6.2 Gm. per hundred cubic centimeters. There is likely to be compensatory hyperparathyroidism, so that in cases in which the main deficiency is in phosphorus and the calcium intake has been adequate, the calcium in the serum may be increased to 12.0 to 12.5 mg. per hundred cubic centimeters. In osteomalacia the reparative mechanism of the bones is normal, so that the amount of alkaline phosphatase in the serum is elevated.

Unfortunately for the problem of differential diagnosis, patients with metastatic disease of bone also are frequently ill nourished, and prolonged observation is often necessary before a multiplicity of diseases can be disentangled. In addition, patients with cancers of the gastrointestinal tract, but without metastases to bone, often have changes in the bones due to faulty absorption of food. It is sometimes helpful in doubtful cases to give large doses of calcium, phosphorus and vitamin D and to follow the Sulkowitch reaction of the urine. If the primary disturbance is calcium deficiency, the excess calcium intake will be stored and the Sulkowitch reaction will not increase. In metastatic cancer of bone the excess calcium cannot be used to repair the defects in the bone and will overflow in the urine.

Senile osteoporosis, a disease described by Albright,[32] is due to a defect in the regenerative mechanism of bone, which in turn is probably caused by the endocrine imbalance of later life. Because of the defect, the normal wear and tear on the bones are not repaired, and severe demineralization results. The disease is much more common in women than in men and usually has an insidious onset dating from the menopause. All findings on chemical examination of the blood are normal, and the Sulkowitch reaction corresponds to the calcium intake. The absence of an elevation in the serum alkaline phosphatase serves to distinguish this condition from osteomalacia and from many metastatic cancers in bone. In patients with senile osteoporosis the defective bone cannot utilize the additional building materials made available by large doses of calcium, phosphorus and vitamin D, and the excess calcium spills promptly into the urine, where it can be detected by an increase in the Sulkowitch reaction.

Hyperparathyroidism.—This condition, known variously as von Recklinghausen's disease and osteitis fibrosa cystica generalisata, is due to the increase in the serum calcium and the lowering of the renal threshold for phosphorus which is brought about by excess parathyroid hormone. Both of these conditions result in the loss of large amounts of calcium and phosphorus in the urine, with corresponding depletion of the stores in the bones. In the typical case there are multiple fibrocystic changes in bone, nephrolithiasis and symptoms of hypercalcemia. The amount of calcium in the serum may be anywhere from the upper normal limits

32. Albright, F.; Smith, P. H., and Richardson, A. M.: Postmenopausal Osteoporosis, J. A. M. A. **116**:2465-2474 (May 31) 1941.

to 18 mg. or more per hundred cubic centimeters; the amount of inorganic phosphorus may be from the lower normal limits down to 1.0 mg. per hundred cubic centimeters. The reaction of the urine to the Sulkowitch test parallels the serum calcium and may be extremely pronounced. The value for serum alkaline phosphatase is elevated, the degree of elevation varying with the extent of the damage to the bone, and sometimes reaching 50 Bodansky units per hundred cubic centimeters. The low serum phosphorus will distinguish hyperparathyroidism from osteolytic metastatic cancer in bone. Inasmuch as borderline changes in the serum calcium and phosphorus may occur from emotional or other temporary causes, the determinations should always be made at least twice on blood samples drawn on different days.

While the typical patient with hyperparathyroidism shows a high value for serum calcium, a low value for serum inorganic phosphorus, a high value for serum alkaline phosphatase and a pronounced reaction to the Sulkowitch test, the disease exhibits many confusing variations. Thus, a patient with acute hyperparathyroidism of recent onset who is on a high calcium diet may have a dangerous hypercalcemia and stag horn calculi in the kidneys but only mild demineralization of bone, the high calcium diet having protected the bone from destruction. On the other hand, a patient with mild disease of many years' standing who is on a low calcium diet may have such extreme demineralization that the amount of calcium in the serum can no longer rise, and may even be below normal. Another complication may be found in cases in which stones have been present in the kidney long enough to cause severe renal insufficiency. In these, the damaged kidney can no longer maintain a low threshold for phosphorus, and the value for serum phosphorus, instead of being below normal, may be high. In these patients, other signs of renal disease are readily discovered. Thus, while in typical cases hyperparathyroidism may easily be distinguished by the chemical composition of the blood from metastatic cancer in bone, this disease is often accompanied by secondary changes which must be taken into account before a differential diagnosis can be arrived at.

It is well known that immediately after a parathyroid adenoma which has been causing hyperparathyroidism has been removed, the patient often goes into acute hypoparathyroid crisis. This is characterized by a rise in serum inorganic phosphorus and drop in serum calcium, the latter condition leading to tetany. Since a satisfactory determination of serum calcium cannot be made in less than six to eight hours after the blood is drawn, there may be a dangerous delay in the institution of therapy. It is, therefore, well to remember that a sudden rise in serum inorganic phosphorus is as reliable an indication of hypoparathyroidism as a sudden drop in serum calcium and that determinations of serum phosphorus can be made in less than an hour.

Osteitis Deformans; Paget's Disease of Bone.—The roentgenographic picture in this condition often resembles that in carcinoma of the prostate metastatic to bone. In osteitis deformans, the amounts of calcium, phosphorus and acid phosphatase in the serum are normal, and the value for alkaline phosphatase is greatly elevated, sometimes reaching 200 Bodansky units per hundred cubic centimeters, although values of 20 to 40 units are more common. If the amount of both the acid and the alkaline phosphatase in the patient's serum is above normal, he has metastasizing carcinoma of the prostate. He may also have osteitis deformans, but this is not likely. If he has a very high value for serum alkaline phosphatase and a normal value for serum acid phosphatase, he probably has osteitis deformans, but this is not

certain, since some patients with metastasizing carcinoma of the prostate have no elevation in acid phosphatase. Nor will a very high alkaline phosphatase in a female patient in itself establish a diagnosis of osteitis deformans, since any condition in which large amounts of new bone are being formed will raise the alkaline phosphatase of the serum. Nevertheless, the amount of alkaline phosphatase in osteitis deformans is often so high as to leave little doubt of the diagnosis, especially for a patient in good general condition and without severe symptoms.

Many observers have found that the serum alkaline phosphatase of patients with osteitis deformans shows little variation over a period of years. My associates

Summary of Chemical Findings in Neoplastic Diseases of Bone

Disease	Serum Acid Phosphatase	Serum Alkaline Phosphatase	Serum Inorganic Phosphorus	Total Serum Calcium	Sulkowitch Reaction of Urine	Urine, Bence Jones Protein	Total Serum Protein
Chondroma, osteochondroma, osteoma, exostosis	.....	Normal	Normal	Normal	.....	.....	.....
Solitary bone cyst	.....	Normal	Normal	Normal	.....	.....	.....
Giant cell tumor	Normal	Normal or slightly raised	Normal	Normal	.....	.....	.....
Osteogenic sarcoma	Normal	Usually high	Normal	Normal	.....	.....	.....
Endothelioma of bone	.....	Normal or slightly raised	Normal	Normal	.....	.....	.....
Reticulum cell lymphosarcoma of bone	.....	Normal or slightly raised	Normal	Normal	.....	.....	.....
Rickets	.....	High	Normal or low	Normal or low	.....	.....	.....
Inflammatory disease of bone	.....	Usually normal	Normal	Normal	.....	.....	.....
Osteolytic metastatic disease	Normal	Normal or moderately raised	Normal or high	Normal or high	Pronounced	Negative	Normal
Osteoplastic metastatic not from prostate	Normal	High	Normal	Normal	Normal	Negative	Normal
Carcinoma prostate metastatic to bone	High in 70% of cases	High	Normal	Normal	Normal	Negative	Normal
Plasma cell myeloma	Normal	Normal or slightly raised	Normal or high	Normal or high	.....	Positive in 60% of cases	Normal to very high
Osteomalacia	Normal	Moderately raised	Normal or low	Usually low	Usually slight	.....	Normal or low
Senile osteoporosis	Normal	Normal	Normal	Normal	Normal	.....	Normal
Hyperparathyroidism	.....	High	Low	High	Pronounced	.....	.....
Osteitis deformans	Normal	High	Normal	Normal	Normal	.....	Normal

and I have confirmed this observation in general, but have found occasional exceptions. A few patients who had shown constant values for serum alkaline phosphatase for several years showed a sudden rise to double the usual value. Simultaneously there was an increase in symptoms, and in 1 patient an osteogenic sarcoma developed. The average osteogenic sarcoma does not contain more phosphatase per gram of tissue than does the bone of osteitis deformans. Hence, the rise in serum phosphatase in this case was probably not due to the presence of the sarcoma, but was an indication of an increase in activity of bone, which in turn led to malignant change. It has also been found that, just as an acute illness

may stop normal growth of bone in a child, so systemic disease may reduce activity of bone in osteitis deformans, with an accompanying drop in serum alkaline phosphatase in both cases.

SUMMARY

The accompanying table summarizes the chemical findings in typical cases of various neoplastic diseases of bone and in the non-neoplastic diseases most likely to be confused with them. The first eight entries show conditions most commonly found in children and young adults; the remainder of the table shows those most frequently found in older patients. Where a space is left blank, detailed studies are lacking, but abnormal values have not been reported.

The members of the Bone, Urological and Breast Departments of the Memorial Hospital for the Treatment of Cancer and Allied Diseases furnished the clinical material presented in this paper.

The Memorial Hospital for the Treatment of Cancer and Allied Diseases.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1942

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

V. INFANTILE PARALYSIS

PREPARED BY LENOX D. BAKER, M.D., AND HOWARD SCHAUBEL, M.D., DURHAM, N. C.

(Continued from page 318)

Introduction.—During these times of war and in the presence of much argument in the lay press as to the therapy of infantile paralysis, it is encouraging to review the excellent studies which have been reported during 1942 on the causation, epidemiology, means of transmission and true pathogenesis of poliomyelitis. Certainly the workers behind the scenes are to be commended for their untiring efforts to establish means of controlling the disease.

Causation, Transmission and Epidemiology.—McClure and Langmuir [102] report the recovery of poliomyelitis virus from the feces of 4 of 5 patients with acute poliomyelitis in a rural community in the state of New York and from the feces of 20 of 27 contacts of the patients. They did not recover the virus from the feces of 4 persons who had histories of having had poliomyelitis in the past or from the feces of 4 persons in the same community who had no contact with the patients. Trask and Paul,[103] continuing their original work, collected samples of unchlorinated sewage from New Haven, Conn., and New York monthly over a period of fifteen months from April 1940 through June 1941. Of forty-five monthly tests for poliomyelitis virus, thirty-six were completed, and thirty-five of these gave negative results. The sample that contained the virus was collected on Sept. 19, 1940, and the test monkey became ill with poliomyelitis on October 1. It is of interest that during the period the tests were made there were remarkably few cases of infantile paralysis in New York and New Haven. The authors feel that the result of their investigation and its relation to cases of poliomyelitis reported adds little to the knowledge of the pathogenesis of poliomyelitis. Their study is of value in that they were unable to detect the virus of poliomyelitis in sewage during nonepidemic periods, and it is likely that the periodic sampling of sewage for pathogenic virus or bacteria may be a method of epidemiologic importance. Howitt, Buss and Shaffrath [104] made examinations of stools in Kern County, Calif., where poliomyelitis has occurred each year in the same geographic area since 1938. Examination of specimens collected in 1941 from 11 patients with onset of the disease in 1939 and from 8 with onset of the disease in 1940 did not show the presence of the poliomyelitis virus.

However, stools from 4 (28.5 per cent) of the 14 patients for whom a diagnosis of poliomyelitis was made in 1941 yielded the virus. Three of these patients lived under rural or semirural conditions, and the active agent was recovered from the privies of 2 families. The virus was obtained from the feces of 1 patient in five,

102. McClure, G. Y., and Langmuir, A. D.: Search for Carriers in Outbreak of Acute Anterior Poliomyelitis in Rural Community: Incidence of Virus in Feces, Am. J. Hyg. **35**: 285-291 (March) 1942.

103. Trask, J. D., and Paul, J. R.: Periodic Examination of Sewage for Virus of Poliomyelitis, J. Exper. Med. **75**:1-6 (Jan.) 1942.

104. Howitt, B. F.; Buss, W. C., and Shaffrath, M. D.: Acute Anterior Poliomyelitis in Kern County, California, Am. J. Dis. Child. **64**:631-648 (Oct.) 1942.

fifteen and twenty-four days but not in thirty-nine or seventy-three days after the onset of the disease and from other patients in five, fourteen and fifty days after the appearance of the first symptom. Undiluted specimens of stools kept for four months at —70 C. contained active virus, while the virus remained viable in frozen untreated feces for periods varying from seven days to five and one-half weeks before being inoculated into monkeys. The feces of 7 (22.4 per cent) of 31 healthy contacts of patients with poliomyelitis gave evidence of the virus when inoculated into monkeys. All contacts except 1 were children. No virus was obtained from nine samples of sewage, from bird and chicken feces or from a limited number of house flies collected during this interepidemic period.

Toomey, Takacs and Tischer [105] set fly traps near the mouth of a brook that emptied raw sewage into Lake Erie. Excrement was plainly visible on the top of the water. This brook drained parts of the northeastern section of the city of Cleveland, where the epidemic first appeared this year—an area in which a large number of cases were found. A large yield of flies was obtained, mostly large blow flies, with only an occasional small house fly and a few wasps and moths. About 2,000 etherized flies were put in a glass bead grinder and prepared for injection into monkeys. Two animals were used, and the disease developed in both. A 10 per cent suspension of the cord of the first animal killed was injected into a third monkey, and the disease was produced. In spite of these results Toomey and his associates feel that the facts were of slight epidemiologic importance, because: (1) in twenty experiments over a ten year period the virus was not obtained from house flies consistently during either epidemic or nonepidemic years; (2) the disease did not always occur in crowded communities infested with flies, but appeared more often in clean surroundings devoid of flies; (3) the peak of the disease and that of the fly population did not correspond.

Lumsden [106] in an epidemiologic study of poliomyelitis in Mississippi noticed that over two thirds of the afflicted persons lived in open country homes. A seasonal prevalence was as follows: 1 case in February, 1 in March, 3 in May, 16 in June, 28 in July, 29 in August, 13 in September and 8 in October. Lumsden concludes that poliomyelitis is spread not by personal contact but by unknown factors. The picture as a whole suggests infection by place rather than by person. His community studies substantiate his conclusions.

Hershey [107] reports public health measures used during the summer of 1941 in Okanagan Valley, British Columbia. Early in the summer prepared circulars stressing the importance of early diagnosis and outlining diagnostic points and methods of prevention and control were supplied to the physicians of the province. Attempts to control the spread of this disease after it had broken out in the district depended almost entirely on rigorous control of sanitation and institution of quarantine for a period of six weeks for all persons known to be contacts. It was concluded that half measures were useless in attempting to control the spread of acute anterior poliomyelitis, but by rigorous efforts the 1941 epidemic was broken off at a time when further cases might have been expected in a district that had suffered heavily in previous outbreaks.

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105. Toomey, J. A.; Takacs, W. S., and Tischer, L. A.: Poliomyelitis Virus from Flies, Proc. Soc. Exper. Biol. & Med. **48**:637-639 (Dec.) 1941.

106. Lumsden, L. L.: Epidemiological Study of Poliomyelitis in Mississippi in 1941, Pub. Health Rep. **57**:729-753 (May 15) 1942.

107. Hershey, J. M.: Outbreak of Acute Anterior Poliomyelitis in Okanagan Valley, British Columbia, Canad. Pub. Health J. **33**:452-460 (Sept.) 1942.

Dauer [108] reports the prevalence of poliomyelitis in the United States in 1941. In 1940 the disease occurred in epidemic form in several large areas in the north central and northwest sections of the country, with rather high rates in West Virginia, Kansas, Minnesota and Michigan. In 1941 poliomyelitis was most prevalent in the eastern, south central and south Atlantic states. Four southern states, Alabama, Florida, Georgia and Tennessee, accounted for approximately one fourth of all of the cases reported in the entire country. In the middle Atlantic states and in Minnesota the incidence of the disease was slightly higher than for the country as a whole. Several investigators studying feces of flies reported recovery of poliomyelitis virus from the flies caught in areas where the disease was prevalent in the summer of 1941.

Susceptibility and Immunity.—Aycock [109] reviews several sets of observations, all of which, under the concept outlined, are consistent with hereditary susceptibility as a factor which determines the occurrence of paralysis in a selected few of the many exposed to the virus. The intensity with which the hereditary susceptibility is exhibited in the distribution of the disease, as indicated by these studies, clearly is not sufficient to afford any basis in itself for controlled measures, but rather forms a background for a study of the nature of individual susceptibility to paralysis and suggests that the search for predisposing causes should include conditions inherent in the constitutional makeup of the patient.

Howe and Bodian [110] point out that it is generally conceded that a relatively substantial and lasting immunity to poliomyelitis is conferred through the invasion of the nervous system by active virus. However, well authenticated second attacks of the disease do occur both in human beings and in experimental animals. The type of immunity which occurs is thought to be a local one, and such immunity of the nervous system may be further restricted to include only portions of it. In 40 rhesus monkeys, intracerebral, intraocular, intracutaneous, intraperitoneal, intraspinal and intraneural inoculations of poliomyelitis virus produced no lesions in the olfactory bulb despite the fact that the animals contracted paralysis. Two monkeys, convalescent from an intracutaneous and intracerebral inoculation respectively, had further paralysis after intranasal inoculation of heterologous virus. A third animal, convalescent from an intranasal inoculation, showed extension of the lesion after intranasal and intraocular inoculation with heterologous virus. Two animals in which the spinal cord had been transected and in which an attack of poliomyelitis was limited to an isolated segment of cord contracted typical paralysis in previously uninvaded portions of the central nervous system after intranasal inoculation of homologous virus. Four of 6 convalescent monkeys showed extension of lesions but no clinical signs after inoculation of homologous virus through a previously uninvaded portal. Four animals convalescent from a unilateral intranasal inoculation showed evidence of new invasion in the opposite olfactory bulb but no extension of paralysis after a second inoculation of homologous virus into the nostril. Two animals had second attacks after a heterologous second inoculation. The intranasal portal was used for both exposures. They conclude that in the rhesus monkey a second attack of poliomyelitis, whether paralytic or not, seems to depend on the strains of virus used and the degree to which the virus is disseminated through

108. Dauer, C. C.: Prevalence of Poliomyelitis in United States in 1941, Pub. Health Rep. **57**:710-716 (May 8) 1942.

109. Aycock, W. L.: Familial Aggregation in Poliomyelitis, Am. J. M. Sc. **203**:452-465 (March) 1942.

110. Howe, H. A., and Bodian, D.: Relation of Fiber Pathways to Local Immunity in Experimental Poliomyelitis, Tr. Am. Neurol. A. **67**:122-124, 1941.

the neuraxis during the first exposure. They feel that the experimental data emphasize the difficulty of neutralizing rhesus monkeys for experiments seeking to clear mechanisms of immunity in man and suggest that human immunity to poliomyelitis does not result from immunization of the central nervous system but rather is a result of some process which prevents infective quantities of active virus from reaching nerve tissue (portal immunity).

Aycock [111] made neutralization test studies using four strains of poliomyelitis virus. He showed that monkeys which had recovered from attacks produced by the H virus regularly neutralized this virus but failed to neutralize the Aycock or the Trask virus. Monkeys that have recovered from attacks produced by both the Aycock and the H strain neutralize both these strains of virus as well as the J strain. Of 4 animals, 1 that had recovered from an attack produced by the H virus and 3 that had recovered from attacks produced by the H virus and the Aycock virus, all failed to neutralize the Trask virus. These tests clearly reveal immunologic differences between these strains of virus and in turn serve to explain the failure of convalescent patients in a school outbreak to neutralize the old laboratory Aycock strain of virus. It is suggested that the momentary immunity status of the patients is represented by the presence of neutralizing antibody to strains to which they have been exposed previously and that the end point of immunity (adult) is represented by the presence of neutralizing antibody to a number of strains.

Pathology.—Sabin [112] deals with three major questions: 1. What are the essential lesions of poliomyelitis, and where are they located? 2. How extensive must these lesions be to produce paralytic disease, and what is the basis for the transitory character of some of the paralysis? 3. What determines the special localization and distribution of the lesions? These questions are answered as follows: 1. The upper motor neurons concerned in initiating voluntary movement may be significantly and predominantly affected. The essential lesions are characterized by perivascular cupping, neuronophagia and focal mesodermal-glial infiltrations in all layers. 2. Edema and its disappearance do not cause transitory paralysis. Instead, in cases of transitory paralysis the segmental distribution of the lesions is spotty and does not affect the major innervation of a given muscle; thus a muscle may have enough innervation to regain normal strength. The lesions must be extensive to cause complete paralysis. 3. The virus is found in certain regions of the nervous system and in the gastrointestinal tract. The part of the central nervous system first to be attacked by the virus is determined by the neural connections from the peripheral tissue from which the virus invades, and its subsequent spread within the nervous system is dependent on the central connections of the neurons in which the greatest proliferation of virus occurred. Sabin concludes that a thorough reinvestigation of the pathologic physiology of poliomyelitis is needed.

Schwartz and Bouman,[113] aided by a grant from the National Foundation for Infantile Paralysis, made an interesting study to determine if spasticity existed in the early stages of poliomyelitis. They made oscillographic records of muscle action currents through a four stage amplifier. Their studies were applied to 7

111. Aycock, W. L.: Immunity to Poliomyelitis: Heterologous Strains and Discrepant Neutralization Tests, Am. J. M. Sc. **204**:455-467 (Sept.) 1942.

112. Sabin, A. B.: Pathology and Pathogenesis of Human Poliomyelitis, J. A. M. A. **120**: 506-511 (Oct. 17) 1942.

113. Schwartz, R. P., and Bouman, H. D.: Muscle Spasm in Acute Stage of Infantile Paralysis as Indicated by Recorded Action Current Potentials, J. A. M. A. **119**:923-926 (July 18) 1942.

patients with infantile paralysis, 3 with spastic paralysis and 3 normal subjects for control. They feel that their results justify the following conclusions: 1. In infantile paralysis spasticity of the muscles exists not only in antagonists of the weakened muscles but in the weakened muscles themselves and in muscles in parts of the body in which clinical symptoms of the disease are not evident. 2. The spasticity is of a reflex nature and is not present in the completely paralyzed muscles. 3. The spasticity can be stronger than the voluntary contraction which the muscle is able to perform, as adjudged by action current. 4. When the strength of the voluntary contraction increases through treatment, the spasticity decreases. Schwartz and Bouman cannot say whether the spasticity is actually responsible for weakening of the muscles or whether it is a phenomenon which is merely another consequence of the disease.

Chown,[114] in discussing the feasibility of some of the present concepts of treating the disease, points out that poliomyelitis is an encephalopoliomyelitis and ganglionitis which gives a background not for a single simple picture of flaccid paralysis but for diverse symptoms and signs, such as incoordination, tremor, variations in clonus and autonomic anomalies, as well as transitory signs and symptoms, temporary paralysis and what is referred to as "mental alienation." Chown points out that one cannot use the known pathologic picture of the disease to justify a refusal to reexamine the clinical picture and states that the whole disease is in need of reassessment. Hipps[115] made a study of the pathologic changes in muscles paralyzed by poliomyelitis. A study was made on muscles the strength of which was known and which had been paralyzed for two years or more. The three most interesting and common microscopic observations were: (1) increased interfascicular fibrosis, (2) atrophy and disintegration and (3) large round cells found in muscle bundles containing atrophic cells. A general comparison of the sections from all of the 94 examined muscles revealed the following significant facts: 1. The age of the patient seems to have no bearing on the microscopic picture of any muscle. 2. The muscles showing fatty replacement changes are uniformly weaker muscles than those showing fibrous replacement changes. 3. Fifty per cent of the muscles examined showed cellular hypertrophy in involved bundles. 4. Sections showing cellular hypertrophy almost invariably were from muscles graded "poor" or better, there being only 1 graded "trace" and none graded "zero."

No newly formed or regenerated muscle cells were found in any section, and the author concludes that a gain in strength by partially paralyzed poliomyelitic muscle does not occur through the formation of new muscle fibers but through an overdevelopment or hypertrophy of remaining undamaged cells. He points out that pathologic changes occurring in muscle following acute anterior poliomyelitis are brought on in two ways, primarily through denervation and secondarily from abnormal variations of tension in the muscle. The cellular changes from denervation begin with atrophy and progress to degeneration, disintegration and changes due to replacement. These pathologic changes occur in muscle cells in exactly the same way when they are due to secondary factors. Too much tension or overstretching results in minute tears, zonal degeneration and subsequent fibrosis. The changes produced are identical with those produced by denervation, and the rate of change is nearly as fast. These secondary abnormalities may cause just as much weakness in a muscle as the changes due to primary denervation.

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114. Chown, B.: Newer Knowledge of Pathology of Poliomyelitis, Canad. Pub. Health J. **33**:276-277 (June) 1942.

115. Hipps, H. E.: Clinical Significance of Certain Microscopic Changes in Muscles of Anterior Poliomyelitis, J. Bone & Joint Surg. **24**:68-80 (Jan.) 1942.

Examination.—Eyre-Brook [116] points out the importance of taking more than one specimen of cerebrospinal fluid in a case of suspected poliomyelitis and calls attention to the necessity for proper interpretation of the observations in the light of the changing picture presented by the spinal fluid. Spinal fluid in acute poliomyelitis shows an early rise in cell count and a late rise in protein content. A single specimen taken at the end of two weeks may give a normal picture, since the increase in the number of cells is almost ended and the increase in the amount of protein may hardly have begun. Studies of spinal fluid from 7 patients are discussed, and the results confirm the author's opinion of the value of repeated lumbar punctures in cases of suspected poliomyelitis.

Carroll [117] made an after-effects survey for poliomyelitis in patients treated at the Orthopaedic Hospital in Los Angeles. His series included patients treated during a period of twenty years. There were over 1,700 patients, and more than 1,500 had recorded checks of the muscles to determine the rate and amount of improvement in muscular strength. It was concluded that when paralysis was not complete an increase in muscular strength was made in the majority of cases. Approximately two thirds of the increase was made during the first six to eight months after onset of the paralysis.

Mayer and Greenberg [118] describe a gravity scale and a swivel table which they have used to evaluate the power of the muscles of the trunk. They hope that the scale and table can be used to learn more about the cause of postural defects, painful backs and scoliosis as well as residual paralysis.

De Sanctis and Green [119] report 2 cases of acute infectious polyneuritis as diagnostic problems during a poliomyelitis epidemic. They point out that clinically the two diseases appear similar but when examined more minutely they do differ. The history of both conditions is usually that of a slow progression of symptoms and signs, although the onset of acute infectious polyneuritis occasionally may be sudden and overwhelming. Both diseases cause hyperesthesia, but in poliomyelitis this is really pain in the muscles brought on by activation and deep pressure. In infectious polyneuritis the patient in addition to having pain in the muscles is hyperesthetic to superficial touch. Both diseases may cause nuchal rigidity and tenderness of the muscles of the back, although these complaints are rare in cases of infectious polyneuritis. The progress of the paralysis is ascending in both conditions, but they differ in their types of involvement. The paralysis of polyneuritis is usually symmetric and bilateral and involves the proximal muscles of the extremities more severely than the distal ones. Involvement of the cranial nerves is limited mainly to the seventh nerve. Paralysis in poliomyelitis is usually segmental and is not necessarily symmetric or bilateral but often unilateral and irregular in distribution. Involvement of cranial nerves may be multiple. The writers point out the importance of differential diagnosis because of the favorable prognosis in infectious polyneuritis for recovery from paralysis, and they emphasize changes in the spinal fluid as a key to the diagnosis. Polyneuritis causes an elevated protein content without a change in cell count, and in anterior poliomyelitis there are both a cellular increase, which very early is polymorpho-

116. Eyre-Brook, A. L.: Cerebrospinal Fluid in Acute Anterior Poliomyelitis, Brit. M. J. **1**:758-759 (June 20) 1942.

117. Carroll, R. L.: Rate and Amount of Improvement in Muscle Strength Following Infantile Paralysis, Physiotherapy Rev. **22**:243-257 (Sept.-Oct.) 1942.

118. Mayer, L., and Greenberg, B. B.: Measurements of Strength of Trunk Muscles, J. Bone & Joint Surg. **24**:842-856 (Oct.) 1942.

119. De Sanctis, A. G., and Green, M.: Acute Infectious Polyneuritis: Diagnostic Problem During Poliomyelitis Epidemic, J. A. M. A. **118**:1445-1447 (April 25) 1942.

nuclear and a little later lymphocytic, and a moderate rise in the value for protein. De Sanctis and Green maintain that this difference in the spinal fluid confirms the diagnosis.

[ED. NOTE.—The authors' favorable prognosis for acute infectious polyneuritis is not altogether in agreement with previous reports in the literature and their interpretations of the spinal fluid changes are not altogether in agreement with the report by Eyre-Brook.[116]]

Hansson,[120] in a report on electromyographic investigation of muscles in anterior poliomyelitis, describes an electromyograph for making oscillometric readings of muscular contractures. He found it possible to pick up and study the action potentials of muscles by means of modern oscillographs and discovered that the oscillogram varies with the power of the muscle to contract and thus provides a definite indication of good, fair, poor and vestigial muscular power as well as of normal and paralyzed muscles. By measuring the length of the curve per second and comparing it with the known millivolt deflection a definite figure for a muscle or a group of muscles may be obtained. Hansson says that "if this type of curve could be obtained by electrocardiograph with adequate amplification, the usefulness is obvious."

Experimental Poliomyelitis.—Toomey and Takacs[121] in studying the portal of entry of poliomyelitis and how it passes into the central nervous system found in trying to repeat the work of Hurst and previous work by Toomey that 10 animals in which the virus had been injected into the sciatic nerve failed to acquire poliomyelitis. They then obtained a different strain of virus and found that animals which received injections of it in the sciatic nerve became ill with the disease. In view of the fact that both strains originally came from Flexner's M. V. strain, they conclude that there may be a quantitative difference in virulence between descendants of the same strain of poliomyelitis virus carried by different laboratories. A difference in quantitative virulence in strains of poliomyelitis virus would easily explain negative results following their injection into peripheral nerves. The results of the experiments support the theory of axonic spread of poliomyelitis virus.

Sabin and Ward[122] inoculated the sciatic nerves of 8 monkeys, all of which became ill with poliomyelitis. Nasal secretions were collected on absorbent cotton plugs every twenty-four hours during the life of the monkeys. The nasal secretions collected during each twenty-four to forty-eight hours from several monkeys were pooled and tested for virus. The tests for the virus all gave negative results. The authors conclude that there was no evidence of centrifugal spread. Thus the finding of the virus in the human pharynx and in the intestines suggests these sites as portals of entry. Postmortem studies of the monkeys revealed no virus in olfactory bulbs, nasal mucosa, tonsils, salivary glands, adrenals, superior sympathetic ganglions, celiac ganglions or small intestine.

Wolf,[123] working with the Jungeblut-Sanders virus, carried out further studies on the possible transmission of the virus of human poliomyelitis to rodents as well

120. Hansson, K. G.: Electromyographic Studies in Poliomyelitis, Arch. Phys. Therapy **23**:261-266 (May) 1942.

121. Toomey, J. A., and Takacs, W. S.: Spread of Poliomyelitis Virus Along Axons of Peripheral Nerves, Am. J. Dis. Child. **63**:467-473 (March) 1942.

122. Sabin, A. B., and Ward, R.: Natural History of Experimental Poliomyelitis Infection: Studies on Centrifugal Spread and Elimination of Virus in Intrasciatically Inoculated Rhesus Monkeys, J. Exper. Med. **75**:107-117 (Jan.) 1942.

123. Wolf, A.: Studies in Rodent Poliomyelitis: Pathology of Murine and Cavian Poliomyelitis, J. Exper. Med. **76**:53-72 (July) 1942.

as to monkeys. Wolf studied the histologic changes of the S. K. rodent virus infection in white mice and guinea pigs submitted by Jungeblut and Sanders. He describes the lesions produced in mice and guinea pigs by inoculation of the virus and states that he has observed that in mice the virus apparently retains its affinity for the anterior horns of the spinal cord, but in a moderate degree. Associated with a marked increase in virulence of the virus, a strong affinity for the cerebral tissues, more particularly the olfactory centers, develops. When this murine variant of the virus is transmitted to the guinea pig, however, its original character is again revealed, and there is a reversion to a predominant affinity for the nerve cells of the anterior horns of the spinal cord.

Kramer, Geer and Himes [124] made studies on the continuous intravenous administration of hypotonic solution of sodium chloride in acute experimental poliomyelitis. They carried out seven experiments using 29 monkeys and conclude that the administration of hypotonic solution of sodium chloride to monkeys infected with poliomyelitis virus does not affect the course of the disease.

Tonsillectomy and Poliomyelitis.—Francis, Krill, Toomey and Mack [125] report a most interesting family incidence of poliomyelitis. The K family of Akron, Ohio, consisted of father, mother and 6 children. The children's ages ranged from 2½ years to 11 years. All the children were healthy on Aug. 1, 1942. On August 22, the 5 oldest children had tonsillectomies and the 4 oldest also had teeth extracted. On August 31 the 7 year old child became ill. By September 5, the 5 children who had been operated on all became ill with severe bulbar poliomyelitis, and 3 died. The father, the mother and the 1 child who had not been operated on showed no signs of illness. During the period the K family had poliomyelitis Akron was relatively free of the disease. The K children had had no contact with other patients with poliomyelitis, and no subsequent epidemic occurred in Akron. A search for possible contacts had remarkable results. The virus was recovered from the stools of 2 cousins living in a city 50 miles (80 kilometers) away with whom the K children had been in contact in June 1941. Four additional cousins in another family group, with whom the K children had lived for two weeks following June 1941, showed virus in their stools but did not get clinical poliomyelitis. No virus was obtained from 9 adult relatives or from cousins of two other family groups with whom contact was casual. Among 28 playmates a group of 3 children in one family was found to be carrying poliomyelitis virus. Toomey and Krill,[126] in another report made from the Children's Hospital in Akron and the division of contagious diseases of the City Hospital in Cleveland, show that 14, or 82 per cent, of 17 patients who had a tonsillectomy and adenoidectomy within thirty days prior to the onset of the illness became ill with bulbar paralysis. Among patients who had not had such operations 7, or 5 per cent, of 140 patients admitted to Children's Hospital and 23, or 19.4 per cent, of 118 patients admitted to City Hospital were stricken with bulbar paralysis. To explain the relationship between poliomyelitis and tonsillectomy Toomey and Krill consider two possibilities: (1) that poliomyelitis occurs as an accident during the course of mass immunization or exposure, during which time most or

124. Kramer, S. D.; Geer, H. A., and Himes, A. T.: Use of Continuous Intravenous Administration of Hypotonic Sodium Chloride (Retan Treatment) in Acute Experimental Poliomyelitis in Monkeys, J. Immunol. **44**:175-194 (July) 1942.

125. Francis, T., Jr.; Krill, C. E.; Toomey, J. A., and Mack, W. N.: Poliomyelitis Following Tonsillectomy in Five Members of a Family: Epidemiologic Study, J. A. M. A. **119**: 1392-1396 (Aug. 22) 1942.

126. Toomey, J. A., and Krill, C. E.: Tonsillectomy and Poliomyelitis, Ohio State M. J. **38**:653-655 (July) 1942.

all persons may harbor the virus and (2) that poliomyelitis has nearly an obligate affinity for gray fibers of either medullated or unmedullated nerves. Operation exposes the axis-cylinders of cut peripheral nerves and thus possibly makes absorption by gray fibers much easier. Or it may be that because of the operation new vascular networks are laid down, a process associated with deposition of new unmedullated fibers of the type which easily absorbs virus. They feel that in their locality it would be advisable to do tonsillectomies in the late spring.

Aycock [127] reviews the literature on tonsillectomy and its relation to bulbar poliomyelitis and presents rather conclusive statistics on 918 cases occurring in Massachusetts from 1927 through 1931 and on 743 cases occurring in Vermont from 1912 through 1931. He concludes that the absence of tonsils does not predispose to the paralysis of poliomyelitis but rather is a determinant as between the spinal and the bulbar type of the disease. From the Massachusetts report it was learned that of 210 patients with bulbar paralysis 122 or 58.1 per cent had had a tonsillectomy. Of the 638 patients with spinal paralysis 146, or 22.8 per cent, had had a tonsillectomy.

Seydell [128] made an exhaustive study of the literature and obtained statistics by addressing a form letter to each state board of health, to the United States Public Health Service and to thirty-five hospitals located in various parts of the country. It is difficult to evaluate his interpretations, since apparently his object in writing the paper was to prove that tonsillectomy does not affect the course of poliomyelitis. He hesitates to accept the full value of the statistics presented by Eley and Flake, with their high percentage of patients with bulbar poliomyelitis who had been tonsillectomized within thirty days, because these statistics take into consideration only those patients who were admitted to a single hospital and do not fully represent all who were included in the epidemic. A survey of the statistics accumulated in Seydell's paper shows that the total number of cases in which bulbar poliomyelitis followed a recent tonsillectomy was 48; the number of cases in which the spinal form of the disease occurred after this operation was 25. That is, there were almost twice as many cases of bulbar as of spinal poliomyelitis, and the author says, "The disparity is striking, and I can offer no explanation for it." [ED. NOTE.—Do the tonsillectomies explain the disparity?]

Early Treatment.—Cadham [129] reports on a method of collection of immune serum by which from June 1 to Sept. 15, 1941 80,000 cc. of blood was collected from 125 donors who had previously suffered from an attack of poliomyelitis. The donors returned at intervals, and from 65 to 120 cc. of blood was withdrawn from each donor each time. The serum was put up in vials containing 20 cc. for intramuscular injection during the preparalytic stage. Cadham stated that the clinical reports indicate that when the convalescent serum was used it was of therapeutic value.

Coggeshall and Maier [130] tested a number of sulfonamide compounds, sulfones and other compounds (principally heterocycles) for their effectiveness against two experimental virus infections in white mice. None of the drugs was effective in

127. Aycock, W. L.: Tonsillectomy and Poliomyelitis: Epidemiologic Considerations, Medicine **21**:65-94 (Feb.) 1942.

128. Seydell, E. M.: Relation of Tonsillectomy to Poliomyelitis, Arch. Otolaryng. **35**:91-106 (Jan.) 1942.

129. Cadham, F.: Convalescent Serum in Poliomyelitis, Canad. Pub. Health J. **33**:287 (June) 1942.

130. Coggeshall, L. T., and Maier, J.: Effect of Various Sulfonamides, Sulfones, and Other Compounds Against Experimental Influenza and Poliomyelitis Infections in White Mice, J. Pharmacol. & Exper. Therap. **76**:161-166 (Oct.) 1942.

delaying or preventing the development of the disease or in reducing the mortality from the infection. They feel that because of the considerable number of compounds tested and because many of them were representative of large groups of related chemicals, the reporting of their negative results is of value.

[ED. NOTE.—The results of this experimental investigation are in keeping with the clinical results that have been obtained in attempts at using sulfonamide compounds in treating virus diseases.]

The Council on Physical Therapy of the American Medical Association [131] has published a pamphlet which graphically sets forth the details for the construction of a simple respirator which was prepared during an emergency in the Michigan epidemic of 1940. The respirator was constructed of two gasoline drums welded together and fitted with a hand-manipulated valve. This apparatus was attached by a hose to the one available respirator as a "trailer." Two children were placed in this "trailer," and women of the community worked the valve on the drums constantly for thirty-six hours until a mechanical automatic valve was made which allowed the homemade respirator to simulate the manufactured Drinker respirator. Details for the construction of the apparatus are available for distribution on application to the Council on Physical Therapy.

McLoughlin [132] discusses the epidemic of poliomyelitis in 1941 in Georgia and points out that many patients have been kept alive by the early and continued use of the respirator. He describes the physics, physiology, technic and indications for use of the respirator and warns as to the contraindications for its use. He feels that the use of the respirator in properly selected cases will give excellent results and will prove of inestimable value. However, if it is used indiscriminately and routinely, without proper selection of patients, the results are bound to be disappointing, and statistically it will appear to be of little value in the saving of human life. On the other hand, a knowledge of the early signs of respiratory failure will permit the use of the respirator long before the weakened muscles have become exhausted. He warns that it must be remembered that bulbar types of paralysis do not as a rule show satisfactory improvement and that they account for the majority of disappointing results to be found after the use of the respirator.

The Kenny Treatment.—Much has been written on the Kenny treatment of poliomyelitis during the year 1942, and it was the chief topic of argument at the recent meeting of the American Academy of Orthopaedic Surgeons. Undoubtedly overenthusiastic lay publicity, personality clashes and a misunderstanding of terminology have prejudiced many physicians against Miss Kenny and her work. If one is interested in getting a fair appraisal of the studies which have been made on the Kenny treatment at the University of Minnesota, Krusen's [133] observations should be read. Dr. Krusen in his report traces the history of Miss Kenny's experiences in getting established in this country and gives many personal sidelights which are of interest. He points out that the Kenny concept of poliomyelitis does not conflict with the accepted idea that there is damage to the anterior horn cells in flaccid paralysis. Miss Kenny maintains, however, that something more than this occurs, that the major symptoms early in the disease are not so much due to flaccid paralysis as to three other symptoms: "muscular spasm," a con-

131. Simple Workable Respirator, report of the Council on Physical Therapy, J. A. M. A. **118**:535 (Feb. 14) 1942.

132. McLoughlin, C. J.: Respirators, and How to Use Them, Arch. Phys. Therapy **23**: 336-340 (June) 1942.

133. Krusen, F. H.: Observation on Kenny Treatment of Poliomyelitis, Proc. Staff Meet., Mayo Clin. **17**:449-460 (Aug. 12) 1942.

dition called "incoordination" and another condition given the descriptive name "mental alienation." "Muscular spasm" is defined as a group of symptoms including fibrillary twitchings (fasciculation), hyperirritability of the muscle to stretching and a more or less chronic state of contraction of the muscle fibers which frequently cannot be overcome even by great force. Krusen states that his own observations have convinced him that such spasm does exist during the early stages of poliomyelitis, that it may be widespread and that it is something more than the result of simple meningeal irritation, as was previously thought. A second major symptom, "incoordination," is described as being principally of two types: (1) that due to the spreading of motor impulses intended for a certain muscle to other muscles or groups of muscles because of such a condition as pain on attempted motion of the involved muscle or inability of that muscle to perform its proper function and (2) that occurring within the involved muscle itself, so that ineffective contraction is produced instead of a coordinated rhythmic contraction producing maximum motion at the insertion of the muscle. The third of the major symptoms mentioned is "mental alienation," which is described as the inability to produce a voluntary, purposeful movement in a muscle in spite of the fact that the nerve paths to that muscle are intact. This is a physiologic block which must be distinguished from the organic interruption resulting from the destruction of anterior horn cells by the disease. As an example of this unusual conception, which is difficult to accept, in a case of foot drop the gastrocnemius muscle is said to be in "spasm" and the dorsiflexor muscles are said to be "mentally alienated." According to this conception, the muscles which usually are spoken of as paralyzed in some instances are not truly so, although they may be, but are "mentally alienated" because of the spasm of the gastrocnemius muscle. It must be remembered that it is not claimed that "spasm," "incoordination" and "mental alienation" are the only mechanisms which are present in poliomyelitis. In an exceedingly severe infection enough anterior horn cells are destroyed at the outset to cause complete flaccid paralysis of certain muscles or parts, and spasm, if present at all, may be fleeting. Treatment for this condition is ineffective in preventing the paralysis. Space will not allow a complete review of Dr. Krusen's description of the treatment of "spasm," "incoordination" and "mental alienation." "Spasm" is treated by hot fomentations and by reeducation of the muscle after spasm is eliminated by focusing the patient's attention on the motion to be performed to establish "mental awareness." Reeducation of muscles depends on the relief of spasm, the teaching of mental awareness, the combating of incoordination and alienation and the retraining of neural pathways back to the nonfunctioning muscles. Dr. Krusen points out that the tremendous enthusiasm for the Kenny procedure seems to a large degree warranted, although it appears evident that some of the claims concerning it are too enthusiastic. He points out that some of the claims, such as "absolutely no deformities," are misleading, since some of the patients do have flail extremities after the Kenny treatment, and some of them walk with a Trendelenburg limp. These are certainly deformities. What the observers probably meant to say was that they had not seen such deformities as contractures and malalinement. Dr. Krusen feels that Miss Kenny's ideas are original, that she should be given full credit for having developed a new and extremely interesting concept of the symptoms of early poliomyelitis and the proper management of these symptoms, and that the Kenny method merits the close scrutiny of every physician.

[ED. NOTE.—Dr. Krusen's observations merit a close reading by every physician.]

Irwin [134] reports on the use of the Kenny therapy at Warm Springs, Ga., and states that the patients in the acute stage of the disease have been more comfortable and have had no limitation of motion in the joints and no contractures or scoliosis and that the period of convalescence has been materially shortened. However, all of these patients, although in good condition, have not been entirely cured of their paralysis. He is still convinced that some patients will always show a residual muscular weakness and that the degree of this weakness will be determined by the extent and distribution of the destruction in the anterior horn cells. Likewise, he feels that it will always be necessary to have permanent apparatus for some of these patients and that some type of surgical treatment designed for rehabilitation will always be done. But it is his hope that this method will offer a means whereby the number of braces that will have to be worn will be lessened and that the number of operations that must be performed will be reduced to a minimum. He states that his presentation can be considered neither an endorsement nor a critical analysis of the method, and he apparently intends to continue to use it with constant study over a sufficient period of time and when sufficient information has been obtained to disseminate it to the medical profession through the proper channels. In the meantime, he feels that it is important to protect the public against any abuse or misuse of this method of treatment.

Many articles have appeared in the literature during 1942 giving reports of the results of the use of the Kenny treatment. The majority of these reports have been in favor of the therapy. Daly and his associates [135] report the treatment of 71 patients. Twenty-eight, 2 of whom were nonparalytic, were treated by the Kenny method. Forty-three, of whom 10 were nonparalytic, were treated by the orthodox method. [ED. NOTE.—Just what the "orthodox" method is, is questionable.] Their conclusions are that the Kenny treatment is the treatment of choice. Pohl [136] reports on the cases of the first 26 patients treated in this country by Sister Kenny. The 26 cases are presented in tabular form, and the data given include the age, name and sex of the patient, the duration of symptoms, the muscles involved, the duration of hospitalization and the results of treatment. The conclusions are that the Kenny treatment should be immediately adopted as the fundamental treatment of poliomyelitis. Ober [137] emphasizes that the management of acute poliomyelitis should represent the combined efforts of the family physician, the orthopedist and a good nurse. He feels that the Kenny treatment is the correct treatment to use and points out that only a person skilled in the technic should use the Kenny treatment, since a greal deal of damage can result from rough handling of patients and unskilled physical therapy. Stimson [138] in a report on the rationalization of the Kenny treatment points out that no treatment of poliomyelitis is satisfactory and that all treatment is directed along lines of symptomatic relief. He calls attention to the fact that there are four

134. Irwin, C. E.: Brief Résumé of Kenny Method of Treating Infantile Paralysis, South. Surgeon **11**:675-677 (Sept.) 1942.

135. Daly, M. M. I., and others: Early Treatment of Poliomyelitis with Evaluation of Sister Kenny Treatment, J. A. M. A. **118**:1433-1443 (April 25) 1942.

136. Pohl, J. F.: Kenny Treatment of Anterior Poliomyelitis (Infantile Paralysis): Report of First Cases Treated in America, J. A. M. A. **118**:1428-1433 (April 25) 1942.

137. Ober, F. R.: Pain and Tenderness During Acute Stage of Poliomyelitis, J. A. M. A. **120**:514-515 (Oct. 17) 1942.

138. Stimson, P. M.: Minimizing After Effects of Acute Poliomyelitis: Rationalization of Kenny Treatment, J. A. M. A. **119**:989-991 (July 25) 1942.

causes of muscular dysfunction in poliomyelitis: (1) primary loss of innervation, which is the only irremediable condition; (2) spasm of surviving muscles and muscle fibers; (3) muscular incoordination, and (4) mental alienation. He agrees that the Kenny treatment is the treatment of choice today, provided that it is given with the full knowledge that no treatment will help dead motor units and that the Kenny therapy will only rescue the muscles from the effects of spasm, muscular incoordination and mental alienation.

Steindler [139] and Steindler, Russin, Sheplan and Wolkin [140] in two most comprehensive and thorough papers reporting the studies at the Iowa Clinic on the use of the Kenny therapy and modifications thereof report the following conclusions: The entire pathologic concept of infantile paralysis must be changed from the old ideas of a purely motor deficiency originating in the anterior horn cells. The motor dysfunction seems to reach much higher and produces a state of confusion which blocks the use of the individual paralyzed muscles and leads to the adoption of complex substitutionary motions. These motions become habitual and are difficult to overcome unless special detailed instructions in training are given to patients along the lines outlined by Sister Kenny. Steindler and his associates do not believe that all fixation or all immobilization should be abandoned. They believe that when they are convinced of the soundness of the newer clinical observations in infantile paralysis, the application of common sense and of general biologic principles will make apparent the proper road of conduct, free from orthodoxy and from radicalism.

Knapp,[141] in a further report on the studies at the University of Minnesota, based on more than two years of observation of the Kenny method of treatment of infantile paralysis, advances several theories as to the causes of muscular spasm, of mental alienation and of incoordination. In considering the possible mechanism for the production of spasm he presents several possible local causes, such as (1) inflammatory or toxic changes in the muscle itself and (2) circulatory changes resulting in localized anoxia, possibly caused by lesions of the sympathetic nervous system. He points out that it is well known that pain fibers in the muscles come entirely from blood vessels, so that local anoxia might explain the muscular tenderness as well as the spasm, and local anoxia if persistent might result in the development of contractures. Changes in the central nervous system may account for the spasm in the muscles: 1. There may be irritative lesions in the spinal cord. 2. Denervated muscle is hypersensitive to acetylcholine, which in infantile paralysis may be abundantly supplied through the uninvolved motor pathways, the sensory nerves and the autonomic endings. Here is an excellent mechanism whereby local spasm could be caused by pathologic change in the cord. 3. The spasm frequently changes rather rapidly in contractures which in time may become irreversible because of fibrous tissue replacement. Mental alienation is explained as probably being fundamentally a physiologic block in conduction, as contrasted with an anatomic block caused by destruction of anterior horn cells. The work of Bulbring and Burn, which showed that under conditions of perfusion impulses applied to the motor roots failed to be transmitted along the sciatic nerve to the gastrocnemius muscle of the dog when the vascular tone became low, and the well known

139. Steindler, A.: Contributory Clinical Observations on Infantile Paralysis and Their Therapeutic Implications, J. Bone & Joint Surg. **24**:912-921 (Oct.) 1942.

140. Steindler, A.; Russin, L. A.; Sheplan, L., and Wolkin, V.: Recent Changes in Concept of Treatment of Poliomyelitis, Arch. Phys. Therapy **23**:325-331 (June) 1942.

141. Knapp, M. E.: Kenny Treatment for Infantile Paralysis, Arch. Phys. Therapy **23**: 668-673 (Nov.) 1942.

condition of paralysis or apparent paralysis of the anterior tibial muscle which disappears after an operation to lengthen a contracted achilles tendon are cited as instances of probable mental alienation. Incoordination is explained as a disturbance in the normal motor patterns as a result of paralysis, alienation or spasm, in which new motor patterns are developed which must be restored to normal before normal action can occur.

[ED. NOTE.—Knapp presents many lines of thought for further investigation on this most interesting subject.]

Cole, Pohl and Knapp [142] outline in minute detail the characteristic spasm and how it is detected in various areas of the body. They also give detailed instructions on the application of the Kenny treatment of spasm and muscle reeducation. Hansson [143] reviews the history of the treatment of poliomyelitis and points out that there are such diversions of opinion in regard to the therapy in poliomyelitis because it is difficult to estimate the relative value of any form of therapy. The basis of evaluation is the muscle-grading system, which varies with each examiner. He points out that Miss Kenny has no clinical data to show and that testimonials cannot be used to convince modern physicians. He feels that the most rational treatment of poliomyelitis is halfway between the early intensive treatment and the long immobilization. Lewin [144] endorses the Kenny therapy, as does Dyson.[145]

Toomey [146] in his usual thorough manner describes the Toomey-Feiss method of treatment, whose salient features include elimination of immobilization, active and passive treatment and general physical therapy of the weak or paralyzed muscles, and manipulation and massage of the opposing stiffened muscles. He emphasizes the importance of early treatment by properly trained persons, under proper guidance. He describes the general treatment in minute detail. It has been adopted through trial and error methods during the past twenty years in treating over 1,400 patients in the acute stage of the disease. He feels that in his locality he could point to the work of one physician specializing in physical therapy whose results would compare favorably with those obtained in any clinic. Dr. Toomey points out that any treatment, early or late, followed by poor physical therapy will give poor results and warns that in being critical one should not lose a sense of proportion and "call a spade a steamshovel." He makes it plain that when one talks of the results of any one treatment only those patients with evidence of damage to the anterior horn cells, whether mild or severe, should be selected to demonstrate its benefit. Toomey discusses the various concepts of the Kenny therapy and states that any disagreement he might have with Miss Kenny is not with her method of treatment. After a week spent at the University of Minnesota observing the patients treated by the Kenny method, he points out that Miss Kenny has an uncanny knowledge of bodily mechanics and the uses to which muscles can be put. He believes that most of her results are due to a superior knowledge of muscle reeducation, in which she is a past master. Toomey does not agree with

142. Cole, W. H.; Pohl, J. F., and Knapp, M. E.: Kenny Method of Treatment for Infantile Paralysis, Arch. Phys. Therapy **23**:399-418 (July) 1942.

143. Hansson, K. G.: Present Status of Physical Therapy in Anterior Poliomyelitis, Physiotherapy Rev. **22**:3-5 (Jan.-Feb.) 1942.

144. Lewin, P.: Kenny Treatment of Infantile Paralysis During Acute Stage, Illinois M. J. **81**:281-296 (April) 1942.

145. Dyson, J. E.: Kenny Treatment of Infantile Paralysis of Acute Stage, J. Iowa M. Soc. **32**:297-298 (July) 1942.

146. Toomey, J. A.: Early Treatment of Poliomyelitis, J. Pediat. **21**:353-373 (Sept.) 1942; Treatment of Infantile Paralysis in Acute Stage, Arch. Phys. Therapy **23**:650-662 (Nov.) 1942.

Miss Kenny's theories but admits that she gets good results with her methods and feels that her classification of muscles is logical and that her meticulous program of reeducation leaves little to be desired in the after-care of infantile paralysis.

McCarroll [147] calls attention to the many glowing reports on the results of treatment of acute anterior poliomyelitis by numerous and widely different forms of physical therapy during the past quarter century. He compares the results of the various forms of treatment in 245 recent cases of poliomyelitis (487 involved extremities) observed at the St. Louis unit of the Shriners' Hospital for Crippled Children between 1935 and 1941. From the findings he concludes that it is safe to assume that the results in anterior poliomyelitis can be more adequately explained on the basis of the underlying pathologic process than according to the form of the early treatment used. His study included no patients treated by the Kenny method, but he states that it has been his privilege to visit briefly the various hospitals in Minneapolis and see some of the patients treated under Miss Kenny's supervision. He believes that for symptomatic treatment in the acute stage this method may offer definite advantage but that it falls far short of supplying the answer to the problem. McCarroll feels certain that the Kenny method in time will take its place among the others offered to the field of physical therapy as having been tried but found wanting. He feels that physical therapy will never prove to be the answer, that the control of poliomyelitis will undoubtedly some day be brought about through prevention and not through cure and that the sooner more of the available funds are used for research work in the field of immunology, the sooner the investment will begin to yield satisfactory returns.

Operations.—The Research Committee of the American Orthopaedic Association [148] in a most excellent report of a survey of end results on stabilization of the paralytic shoulder summarizes the results for 148 patients, of whom 101 had shoulder fusions. The average position of fusion in this series was 40 degrees abduction, 10 degrees flexion and 40 degrees internal rotation. The average active rotation of the scapula was 70 degrees. The committee believes that the best position for fusion, if there is fair to good power in both the trapezius and the serratus anterior muscle, is 45 to 55 degrees of abduction, 15 to 25 degrees of flexion and 15 to 25 degrees of internal rotation. In analyzing the position for fusion they point out that a greater range of motion of the scapula develops in children than in adults. The proper function of fused shoulders depends on good power in the upper part of the trapezius muscle and the upper two thirds of the serratus anterior muscle. The trapezius starts abduction, and the serratus anterior finishes it. When the serratus is powerless the trapezius can abduct only 45 degrees. The range of motion is better in patients operated on when under 12 years of age, and the operation can be done any time after the patient is 6 years of age. A majority of the shoulders were fused by the operation described by Gill, and the average time of immobilization in plaster was three and one-half months. The committee concludes that arthrodesis of the shoulder is the operation of choice in all cases of poliomyelitis in which there is complete paralysis of the deltoid muscle.

147. McCarroll, H. R.: Role of Physical Therapy in Early Treatment of Poliomyelitis, J. A. M. A. **120**:517-519 (Oct. 17) 1942.

148. Survey of End Results on Stabilization of Paralytic Shoulder, report of Research Committee of American Orthopaedic Association, J. Bone & Joint Surg. **24**:699-707 (July) 1942.

Williamson, Moe and Basom [149] report the results of the use of fascial transplants for paralysis of the abdominal muscles as described by Lowman. Their study includes 31 operative procedures on 29 patients, all of whom had some degree of paralysis of the abdominal wall as a result of poliomyelitis. Seven of the patients had been operated on from six to ten months before the report was written, 7 one year, 4 two years, 4 three years, 3 five years, and 4 six years. The authors conclude that the operation is worth while from the standpoint of stabilizing the abdominal wall, that the patient's fatigue is lessened, that control of the function of the bladder and the bowels is improved, that sitting and walking can be performed better and that the gait is improved. However, the operation did not prove to be of value in the prevention of scoliosis.

Irwin,[150] in describing a controlled method of operative correction for genu recurvatum resulting from poliomyelitis, discusses the types and causes of genu recurvatum following poliomyelitis and describes a technic of osteotomizing the upper end of the tibia and fibula, with control of the fragments by the use of a Kirschner wire in the proximal fragment to hold it in hyperextension while the lower fragment is carried posteriorly for realinement. The operation is done through two incisions, and the knee joint is not disturbed.

[ED. NOTE.—This operation appears to be a simple procedure with sound mechanics which gives one perfect control over the fragments.]

VI. NEUROMUSCULAR DISORDERS EXCLUSIVE OF INFANTILE PARALYSIS

PREPARED BY WINTHROP M. PHELPS, M.D., BALTIMORE

During 1942 there was a definite decrease in the volume of literature dealing with neuromuscular disorders. This was to be expected, because of the great necessity for interest in the problems of military medicine and the diversion of research into the specific problems of war. The work in the field of war injuries with neuro-orthopedic complications has not progressed far enough for any end results in this field to be published. For example, there were no articles on neurologic injuries to the spine, although such injuries are certainly being seen as the war progresses. The more acute phases of such conditions are probably being discussed in connection with war injuries in general.

The references in this field can be classified under five headings: (1) injuries to the peripheral nerves, (2) cerebral palsy, (3) paralysis of the brachial plexus, (4) tabetic arthropathies and (5) muscular dystrophy.

Injuries to the Peripheral Nerves.—McMurray [151] points out the uses and abuses of splints and corrective apparatus in the treatment of injuries of the nerves. The incorrect application of a splint or the use of a splint without regard to the type of neural involvement is too often carried out. Highet [152] also describes the proper splinting for injuries of peripheral nerves.

Hudson [153] describes a method of transplanation of the external peroneal nerve after injury. This nerve is easily injured because of its superficial course

149. Williamson, G. A.; Moe, J. H., and Basom, W. C.: Results of Lowman Operation for Paralysis of Abdominal Muscles, Minnesota Med. **25**:117-120 (Feb.) 1942.

150. Irwin, C. E.: Genu Recurvatum Following Poliomyelitis: Controlled Method of Operative Correction, J. A. M. A. **120**:277-280 (Sept. 26) 1942.

151. McMurray, T. P.: Uses and Abuses of Splints and Other Instruments in Treatment of Nerve Lesions, Brit. J. Phys. Med. **5**:20-42 (Feb.) 1942.

152. Highet, W. B.: Splintage of Peripheral Nerve Injuries, Lancet **1**:555-558 (May 9) 1942.

153. Hudson, O. C.: Lesions of External Peroneal Nerve: Relief by Transplantation, J. Internat. Coll. Surgeons **5**:223-224 (May-June) 1942.

around the head of the fibula. He resects the upper portion of the fibula, allowing the nerve to take a shorter route, especially when correction of genu valgum is indicated surgically. This procedure is especially indicated for persistent pain over the distribution of the external peroneal nerve. He reports 4 cases in which relief of pain was secured.

Maurer [154] describes the complications and sequels of fractures with concomitant injuries to the peripheral nerves in general, and Marques Tourinho [155] reports cases of specific lesions of the radial nerve complicating fractures of the humerus. Kernwein and Lyon [156] describe an interesting complication of complete severance of the sciatic nerve in which a neuropathic arthropathy of the ankle developed.

Cerebral Palsy.—Green and McDermott [157] have made an extensive study of 421 orthopedic operations on 160 patients with spastic paralysis carried out over the past fifteen years. They carefully limited the number of patients operated on, because:

(a) Surgical procedures are an adjunct in the general plan of treatment of cerebral palsy.
(b) Orthopedic operations on patients with extrapyramidal cerebral palsy [athetosis for example] are not often helpful.
(c) Operations are indicated in only a certain proportion of cases of spastic paralysis depending on the nature of the deformity and the general status of the patient.

Within these wise limitations, they found that arthrodesis for deformities of the feet produced the greatest number of good results. There were many good results from the lengthening of the heel cord and transplantation of muscles, provided certain principles were observed.

Lengthening of the hamstring tendons was more successful when it was accompanied with lengthening of the upper end of the gastrocnemius muscle. The results of obturator neurectomy with adductor myotomy were disappointing. Division of the branch of the median nerve to the pronator teres was helpful in correcting pronation, and transplantation of the flexor carpi ulnaris to the flexor carpi radialis corrected both the flexion and the pronation deformity of the wrist. They state that many poor results were due to inadequate postoperative care and training.

Denhoff and Bradley [158] discuss the use of curare in the therapy of cerebral palsy. The treatment of cerebral palsy consists essentially of muscle training combined with physical reeducational procedures. The use of curare produced improved relaxation and reduction of spasticity lasting about four days, which accelerated the response to the muscle training and reeducational program.

Carlson [159] describes cerebral palsy in general and details the treatment of the spastic, ataxic and athetoid types. He emphasizes the necessity for visual training and suggests the use of the microphone and loud speaker in speech training. He also emphasizes the great necessity for thorough academic education.

154. Maurer, J. F.: Injuries to Peripheral Nerves, J. Indiana M. A. **35**:620-622 (Nov.) 1942.

155. Marques Tourinho, M.: Fractures of the Humerus and Lesions of the Radial Nerve, with Report of Cases, Rev. brasil. de ortop. e traumatol. **3**:144-153 (Jan.-Feb.) 1942.

156. Kernwein, G., and Lyon, W. F.: Neuropathic Arthropathy of Ankle Joint Resulting from Complete Severance of Sciatic Nerve, Ann. Surg. **115**:267-279 (Feb.) 1942.

157. Green, W. T., and McDermott, R. J.: Operative Treatment of Cerebral Palsy of Spastic Type, J. A. M. A. **118**:434-440 (Feb. 7) 1942.

158. Denhoff, E., and Bradley, C.: Curare Treatment of Spastic Children: Preliminary Report, New England J. Med. **226**:411-416 (March 12) 1942.

159. Carlson, E. R.: Treatment of Infantile Cerebral Palsy, Northwest Med. **41**:160-163 (May) 1942.

Ross, Norfleet and Löwenbach,[160] who have studied the electroencephalogram in cases of cerebral palsy, show that it may give information regarding the localization and extent of cerebral lesions but that it is not of additional clinical diagnostic value and gives no additional information whatever regarding intelligence. It probably has value for determining susceptibility to convulsive seizures.

Johow [161] and Baker [162] have contributed independently to the therapy of cerebral palsy and Phelps [163] points out the increased improvement in cerebral palsy when there is a close relation between physical therapy and occupational therapy in the general treatment. Each type of therapy supplements the other, while neither is sufficient for the entire program.

Paralysis of the Brachial Plexus.—Caritat [164] describes the surgical and other general orthopedic procedures in the care of obstetric paralysis. Patterson [165] also discusses this subject.

Tabetic Arthropathies.—Despontín and Corsellas [166] describe fractures of the calcaneum and present a case of tabetic arthropathy of the knee with spontaneous fracture of the calcaneum.

Muscular Dystrophy.—Keith [167] presents a careful study of the effects of administration of vitamin B_6 (pyridoxine hydrochloride) on patients with pseudohypertrophic muscular dystrophy. Although doses of from 50 to 500 mg., administered hypodermically, were used, none of the patients showed any improvement in muscular strength. In some, according to the case reports, there was no advancement of the dystrophy during the period of observation, but in most there appeared to be no change whatever in the progress of the disease.

Pohl and Baethke [168] have presented the results of vitamin E therapy (oral) in 15 cases of progressive dystrophy without appreciable results in the control of the condition. For other reports in this field, reference is made to the paper of Cordero.[169]

Hawke [170] investigated also the effects of vitamins B and E in the dystrophies. In 7 cases vitamin B_1 (thiamine hydrochloride), a placebo, pyridoxine hydrochloride, alpha tocopherol (series A) and alpha tocopherol (series B) were tried in succession. Negligible results were obtained with all the materials used, and some subjective improvement was noticed with the placebo as well as with the vitamins.

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160. Ross, I. S.; Norfleet, G. M., and Löwenbach, H.: Cerebral Palsy and Electroencephalogram, South. Med. & Surg. **104**:613-616 (Nov.) 1942.

161. Johow, A.: Therapy of Little's Disease, Rev. chilena de pediat. **13**:337-342 (April) 1942.

162. Baker, F.: Physical Therapy in Cerebral Palsy, Arch. Phys. Therapy **23**:473-481 (Aug.) 1942.

163. Phelps, W. M.: Correlation of Physiotherapy and Occupational Therapy in Treatment of Cerebral Palsy, Occup. Therapy **21**:152-156 (June) 1942.

164. Caritat, R. J.: Surgery and Orthopedics in Nervous Disorders of Childhood, Rev. chilena de pediat. **13**:352-361 (April) 1942.

165. Patterson, R. L., Jr.: Obstetrical Paralysis, Arch. Phys. Therapy **23**:83-88 (Feb.) 1942.

166. Despontín, A. E., and Corsellas, M. F.: Tabetic Arthropathy of the Knee with Spontaneous Fracture of Calcaneum: Case, Rev. méd. latino-am. **27**:606-612 (March) 1942.

167. Keith, H. M.: Vitamin B_6 (Pyridoxine Hydrochloride) in Treatment of Pseudohypertrophic Muscular Dystrophy Among Children, J. Pediat. **20**:200-207 (Feb.) 1942.

168. Pohl, J. F., and Baethke, D.: Vitamin E in Progressive Muscular Dystrophy: Failure of Oral Administration in Fifteen Cases, Am. J. Dis. Child. **64**:455-461 (Sept.) 1942.

169. Cordero, J.: Pseudohypertrophic Progressive Muscular Dystrophy, Bol. Asoc. méd. de Puerto Rico **34**:211-217 (June) 1942.

170. Hawke, W. A.: Vitamin Therapy of Muscular Dystrophy, Canad. M. A. J. **47**:153-155 (Aug.) 1942.

The author concludes: "In no cases did any definite improvement occur."

[ED. NOTE.—In the last three years much attention has been given to the use of vitamin B_6 (pyridoxine hydrochloride) and vitamin E (alpha tocopherol), mainly because of the similarity of vitamin B and E deficiencies in rats and other experimental animals to the dystrophies and myasthenias in man. However, the great preponderance of evidence, which seems to be increasing, is to the effect that little, if any, demonstrable improvement has resulted from the use of either vitamin B_6 or vitamin E alone or from the combination of the two. The importance of these vitamins should be kept in mind, however, since occasionally conditions actually due to deficiency may be encountered which rather closely resemble the dystrophies and for these, of course, administration of the vitamins would prove effective.]

VII. TUMORS OF BONE AND OF SYNOVIAL MEMBRANE

PREPARED BY HENRY W. MEYERDING, M.D., ROCHESTER, MINN.

Tumors of Synovial Membrane.—Gross and Cameron [171] report a case of "synovialoma." Including theirs, the literature contains reports of 49 cases in which a tumor has been derived from the synovial membrane. In 1936 Knox collected 22 cases of this type of tumor and added 3 of her own. Berger, in 1938, collected 24 cases and reported 5 of his own. A year later, in 1939, Coley and Pierson reported 15 cases, and since that time 4 more cases have been added. Synovial tumors have been termed "synovioma," "synovialoma," "synovial sarcoma," and "synovial sarco-endothelioma." In the majority of cases the tumor is malignant. Metastasis may occur five to ten years after excision of the tumor. In the case reported by Gross and Cameron, the patient was a white American woman 57 years of age. The synovialoma had arisen from the suprapatellar pouch. It apparently had been growing for thirty years, and its cellular features indicated that it was benign. The patient was alive five years after excision of the tumor.

Briggs [172] discusses 9 cases of synovioma records of which are on file at the Army Medical Museum. This series includes tumors arising from the articular capsule, the bursal wall and the tendon sheath. Lawrence Smith was the first to group such tumors together because they had a synovial lining. The growth may arise from the outer layer of the synovial membrane, which is composed of dense fibrous connective tissue. If so, it may be hard to distinguish it from fibrosarcoma. It also may arise from the inner layer, which is more cellular and is thought to secrete synovia. In the latter instance the tumor is prone to produce villi. The 9 tumors reported on occurred when the patients were 17 to 42 years of age. Four of the patients were males and 5 females. A history of mild trauma was present in 3 cases. The majority of the tumors were situated in the lower extremity; 5 were situated about the knee, 2 about the ankle, 1 in the foot and 1 in the forearm. The importance of detailed gross and microscopic examination of the tumor at the time of operation is stressed. In none of the cases was the diagnosis made preoperatively. There was nothing characteristic about the history or the clinical appearance of the synovial membrane. Briggs believes that complete excision of the tumor is the method of choice when it appears encapsulated and it can be removed together with a margin of healthy tissue. If complete excision cannot be carried out without injury to important structures, amputation should be per-

171. Gross, P., and Cameron, D. W.: Synovialoma, Arch. Path. **33**:687-690 (May) 1942.

172. Briggs, C. D.: Malignant Tumors of Synovial Origin, Ann. Surg. **115**:413-426 (March) 1942.

formed. He further states that it is difficult to evaluate the result of radiation therapy for this type of lesion but that it seems a reasonable adjunct to excision.

Sutter and Levy Boladeres [173] state that some synoviomas which recur after operation can be considered benign. The subsequent clinical course and histologic appearance are similar to those of other benign tumors, namely xanthoma, fibroma and chondroma. These do not invade neighboring tissues. He reports a case in which the tumor behaved like a malignant tumor. He says that this type of synovioma does occur, although it is observed less frequently than the benign type. He says that in the course of operation the surgeon should observe whether the tumor arises from the synovial membrane. Any tumor which involves a joint, tendon or serosal membrane should be carefully studied microscopically after confirmation of malignancy. The tumor should be treated surgically because radiotherapy has proved to be inadequate for tumors of this type.

Haggart [174] reports a case of synovioma of the knee joint in which a diagnosis of cystic swelling of the lateral region of the left knee had been made before operation. The tumor was exposed by an elliptic incision, which left intact the skin directly over it. The adherent cystic mass was separated from the deep fascia, the capsule of the knee joint, the periosteum over the head of the fibula and the common peroneal nerve. A tail-like projection entered the knee joint posterior to the collateral ligament; a portion of the capsule, the external semilunar cartilage and the portion of the synovial membrane from which the tumor had originated were excised. In order to close the defect created by the excision, a "releasing" incision was made and Thiersch skin grafts were applied to the secondary wounds. The patient was walking with crutches on the twelfth day after operation, returned to work during the sixth week and has remained well for more than eight years.

A case of chondromatous metaplasia of the synovial membrane of the knee is reported as 1 of the Cabot cases.[175] The patient sought medical advice because of pain and swelling of the knee of nine months' duration. There had been no limitation of motion until two weeks before the patient was seen, when the knee had become stiff. There were no systemic reactions except malaise. The knee was swollen and hot; there was tenderness in both tibiofemoral fossae; the lymph nodes in both groins were swollen but not tender. Laboratory tests did not reveal any abnormality. Roentgenographic examination disclosed finely granular calcification along the lateral margin of the left knee joint. Aspiration obtained slightly cloudy, orange-colored synovial fluid. The fluid contained a normal amount of mucin and numerous erythrocytes and leukocytes. At operation the knee joint was found to be packed with split pea–sized pearly masses, some of which were attached to the synovial membrane. These were removed and synovectomy was performed. Microscopic examination showed that the masses were composed almost entirely of cartilage, and cartilaginous foci were present within the synovial membrane. When the foci developed in the villi they sometimes became pedunculated and sometimes broke off and formed joint "mice."

O'Donoghue [176] reports a case of xanthoma of the knee in which a preoperative diagnosis of fracture of the medial meniscus was made. The tumor was solitary,

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173. Sutter, R., and Levy Boladeres, J.: Synovioma of Wrist, Bol. Liga contra el cáncer **17**:193-200 (July) 1942.

174. Haggart, G. E.: Synovioma of Knee Joint: Case Report, J. Bone & Joint Surg. **24**:438-442 (April) 1942.

175. Chondromatous Metaplasia of the Synovia of the Knee Joint, Cabot Case 28122, New England J. Med. **226**:500-501 (March 19) 1942.

176. O'Donoghue, D. H.: Case of Xanthoma of Knee Joint, J. Bone & Joint Surg. **24**: 940-941 (Oct.) 1942.

pedunculated and well delineated. He points out the extreme similaritiy of the symptoms of discrete tumors to those of rupture of the medial meniscus.

Charache [177] reports 65 cases of tumor of the tendon sheaths. The tumors were classified as ganglion in 60 cases, as lipoma in 2 cases and as hemangioma, fibroma and spindle cell sarcoma in 1 case each.

Localized Cysts of Bone.—Alldredge [178] evaluates the results of various forms of therapy in 152 cases of localized fibrocystic disease of bone. His survey denotes that only two methods of treatment are indicated in cases in which the lesion is operable: (1) resection and (2) bone grafting after curettage of the cystic cavity. Irradiation should be reserved for cases in which the lesion is inoperable. He reports 2 cases in which neoplastic changes occurred many years after the use of radiation therapy. Disturbances and arrest of epiphysial growth commonly occurred after treatment by irradiation.

Jaffe and Lichtenstein [179] describe solitary unicameral cyst of bone as an independent and distinct lesion and do not regard it as a phase of fibrocystic disease of bone. It is uncommon, occurs during childhood or adolescence and affects long tubular bones, especially the upper part of the humerus. It contains fluid, causes a thinning and expansion of the cortex and is lined by thin connective tissue. These authors report 19 cases. Fourteen of the patients were males. In 9 of the cases the lesions were situated in the upper part of the humerus and in 4 the upper part of the femur was involved. Clinically, patients have little or no pain, and the cyst attains a large size before it is discovered or before pathologic fracture occurs. It is most commonly situated in the upper end of the diaphysis near the epiphysial line; it rarely, if ever, goes beyond it. As the acute stage subsides, the cyst appears to become displaced farther away from the epiphysial plate and may move several inches in the course of a few years. It is in the latent and static stage that healing occurs most promptly following operation. Such a lesion cannot be readily distinguished roentgenologically from fibroma, enchondroma or localized fibrous dysplasia. In discussing the pathogenesis the authors subscribe to the theory of Pommer that solitary cyst of bone results from encapsulation and alteration of a focus of intramedullary hemorrhage.

Bick [180] says that some solitary cysts may be early manifestations of a generalized disease. He stresses the value of the clinical history and findings. He has not been favorably impressed by aspiration biopsy and says that examination of frozen sections is reliable for determining the malignancy or benignancy of the lesion.

[Ed. Note.—Aspiration biopsy frequently fails to supply satisfactory tumor tissue. Incision and removal of a section of typical tumor tissue is much more dependable, and examination of frozen sections has been found fairly satisfactory.]

Ferrari [181] reports a case of simple cyst of the tibia in which the patient was 17 years of age. With the patient under spinal anesthesia, the cavity was evacuated and the wall adjacent to the cyst was removed. The wound was closed without

177. Charache, H.: Tumors of Tendon Sheaths, Arch. Surg. **44**:1038-1052 (June) 1942.

178. Alldredge, R. H.: Localized Fibrocystic Disease of Bone: Results of Treatment in One Hundred and Fifty-Two Cases, J. Bone & Joint Surg. **24**:795-804 (Oct.) 1942.

179. Jaffe, H. L., and Lichtenstein, L.: Solitary Unicameral Bone Cyst, with Emphasis on the Roentgen Picture, the Pathologic Appearance and the Pathogenesis, Arch. Surg. **44**: 1004-1025 (June) 1942.

180. Bick, E. M.: Differential Diagnosis of Solitary Cystic Areas in Bone, J. Mt. Sinai Hosp. **8**:1225-1231 (March-April) 1942.

181. Ferrari, R. C.: Simple Cyst of Tibia: Case with Recovery After Surgical Therapy, Bol. d. Inst. clín. quir. **18**:396-401 (June) 1942.

drainage; the patient was observed for four years. At the end of this time it was found that the cavity had been replaced by bone and the defect could not be noted. He states that Ivanissevich reported a case of simple cyst of the femur complicated by fracture. He emphasizes that fracture through a cyst will frequently result in cure because the callus obliterates the cavity and says that a cyst may occur after fracture. Furthermore, he mentions a case of cyst of the tibia that was reported by Nicolini. The patient was 22 years of age. Radiotherapy had been tried without beneficial result. After curettement and evacuation of the cavity and packing with iodoform gauze, the lesion completely healed.

Ortiz Tirado [182] says that formerly surgeons thought that any loose bone should be removed in order to prevent formation of sequestrums. In inexperienced hands, there was abuse of this principle in cases of comminuted fracture. He states that even in recent years he has seen removal of fragments which caused a severe problem in determining the type of treatment for the loss of bone substance. He advocates the use of catgut, kangaroo tendon and wire to hold the fragments firmly in place. He says that he has had no trouble in obtaining union. He does not use plates for fixation, because they are a source of postoperative periosteal pain. He advocates the use of bone chips to fill cavities that have been formed by curettement of bone. He reports 1 case of generalized osteitis fibrosa cystica of the femur in which he curetted the cystic cavity and filled it with bone chips. The patient did not have any pain. Ortiz Tirado says that fragments of bone should not be used if infection is present. In a clean wound, however, every small fragment will help form good callus.

Hand-Schüller-Christian Disease (Eosinophilic or Solitary Granuloma).—Green and Farber [183] have collected 10 cases of this condition. In all of these cases the patients were children less than 12 years of age. In 6 cases the lesions were multiple, and in 4 they were single. The authors describe the condition as a benign destructive lesion of bone and state that the roentgenographic contour of the lesions was variable and usually consisted of a "punched-out" effect. The cortex was not expanded, and there was minimal reaction of bone about the lesion. The flat and irregular bones and the bones of the extremities closest to the trunk were almost always involved. The distribution and appearance of multiple lesions resembled those of metastatic malignant lesions and of multiple myeloma. Single lesions simulated a cyst of bone, osteomyelitis or a malignant lesion. Symptoms were attributable wholly to the local lesion; that is, they consisted of pain and swelling. There was no particular systemic reaction. Laboratory findings were all within normal limits except for the presence of eosinophilia of a mild degree. The microscopic picture usually is as follows: In cases in which the lesions were observed in an early stage of development, destruction of bone and cellular infiltration were observed. The cells of the infiltrate were predominantly mature eosinophils or eosinophilic myelocytes and large mononuclear cells. A variable number of plasma cells, lymphocytes and polymorphonuclear leukocytes were present. The scarlet red stain revealed stainable lipid, but tests for sphyngomyelin were negative. In cases in which the lesions were advanced, eosinophils were not present in the infiltrate. There was a fibroblastic reaction. Large vacuolated mononuclear cells predominated and later might be identical with the "foam" cells of a typical xanthoma. Treatment in this series of cases consisted of roentgen therapy, partial excision and curettage. Most lesions responded to small doses of roentgen rays.

182. Ortiz Tirado, A.: Bone Tissue as Filling Material in Loss of Substances, Cir. y cirujanos **10**:65-70 (Feb. 28) 1942.

183. Green, W. T., and Farber, S.: "Eosinophilic or Solitary Granuloma" of Bone, J. Bone & Joint Surg. **24**:499-526 (July) 1942.

Spontaneous healing occurred in 2 cases. Nine patients seemed entirely well after an average follow-up of more than six years, and 1 died of unknown cause. The authors state that the disease is "not a distinct new entity, but a variant of the basic process of which the clinical pictures known as Hand-Schüller-Christian's disease and Letterer-Siwe's disease are other examples."

In an article entitled "Eosinophilic Granuloma and Certain Other Reticulo-Endothelial Hyperplasias of Bone," Gross and Jacox [184] present the following conclusions:

1. Eosinophilic granuloma of bone is not a new nor distinct entity. It is a reticuloendotheliosis and is probably identical with those cases of Hand-Christian's disease which have been reported to have had solitary lesions. It is also closely related to certain other reticuloendothelial hyperplasias.

2. The interrelationship demonstrated between eosinophilic granuloma and solitary xanthoma of bone, Hand-Christian's and Letterer-Siwe's disease and the existence of cases with features intermediate between these so-called entities make a sharp distinction between them of doubtful validity.

3. Since there are no pathologic, roentgenographic or other decisive features known at present which are distinctive for any one of those reticuloendothelioses, the need for further study, including routine biopsy, in this type of cases is apparent.

Thurm [185] reports a case of eosinophilic granuloma of bone in which multiple osseous lesions were present. The only other case of multiple eosinophilic granulomas of bone was reported by Farber, but he chose to designate the disease as a form of Hand-Schüller-Christian disease. In the case reported by Thurm, lesions were found in both femurs and in four ribs. A low grade fever, moderate leukocytosis and a moderately increased sedimentation rate were the only other essential findings. The lesions showed a tendency to heal spontaneously as well as after curettage. The roentgenographic appearance of the lesions rules out some types of chronic osteomyelitis, metastasis of a malignant tumor and Ewing's tumor.

Benign Osteogenic Tumors.—Osteoma: Horwitz [186] presents a case of osteoid-osteoma (Jaffe-Lichtenstein) of the right astragalus. The patient was a boy 16 years of age. Horwitz mentions that this lesion may be clinically and roentgenographically interpreted as osteomyelitis or as abscess of bone. It usually is unassociated with fever or with increased local heat. Clinical laboratory findings usually are normal. The roentgenogram usually demonstrates a radiolucent area in the bone. Proliferation of bone depends on the site of the lesion. Osteosclerosis may dominate the picture and lead to a mistaken diagnosis of sclerosing nonsuppurative osteomyelitis of Garré or intracortical abscess of bone. Jaffé interpreted the pathologic features as those of benign osteogenic tumor of bone. There usually is a proliferating, vascular osteoblastic tissue with occasional osteoclasts; later there is osteoid tissue which undergoes calcification.

Barron [187] reports a case of osteoid osteoma of the right os calcis. After excision complete cure apparently was obtained. He states that the history of persistent pain that was relieved by acetylsalicylic acid, the roentgenologic appearance and the dramatic relief of pain following excision are all typical of the condition. Furthermore, he states that owing to roentgenologic findings, the condition has been mis-

184. Gross, P., and Jacox, H. W.: Eosinophilic Granuloma and Certain Other Reticulo-Endothelial Hyperplasias of Bone: A Comparison of Clinical, Radiologic and Pathologic Features, Am. J. M. Sc. **203**:673-687 (May) 1942.

185. Thurm, A. S.: Eosinophilic Granuloma of Bone: Report of Case with Multiple Bone Lesions, Bull. Hosp. Joint Dis. **3**:9-16 (Jan.) 1942.

186. Horwitz, T.: Osteoid-Osteoma of the Astragalus, Radiology **39**:226-228 (Aug.) 1942.

187. Barron, L. J.: Osteoid-Osteoma of the Right Os Calcis: Case Report, Bull. Hosp Joint Dis. **3**:141-145 (Oct.) 1942.

labeled "chronic osteomyelitis with a bone abscess or with an annular sequestrum," "sclerosing nonsuppurative osteomyelitis of Garré" or "intracortical disease of bone."

[ED. NOTE.—Further study of this group of tumors will have to be made and a larger series of cases will have to be observed over a period of years before there is a thorough understanding of the lesion.]

Chondroma: Jaffe and Lichtenstein [188] give the name "benign chondroblastoma of bone" to a rare lesion previously called "calcifying" or "chondromatous variant of giant cell tumor" or "chondrosarcoma" or "osteogenic sarcoma." The tumor starts in an epiphysis of some long bone and may extend to the articular surface of the epiphysis and even into the metaphysis; however, it rarely obtains a diameter of more than 3 to 5 cm. Other authors have found that this lesion has a predilection for the upper part of the humerus, but Jaffe and Lichtenstein did not find this to be so. Males predominate, and the patients are almost always in adolescence or past adolescence when seen. The roentgenographic appearance is helpful in making a clinical diagnosis. They describe the pathologic changes in detail and say that the most distinctive feature is the presence of focal areas of calcification of the cellular tumor tissue. Multinucleated giant cells and basic polyhedral cells or round cells with fairly large nuclei were found. The lesion is benign and heals without recurrence after curettage, even without supplementary irradiation. The tumor should not be regarded as a giant cell variant, since the tumor cells are chondroblasts and the tumor is a benign chondroblastoma.

Gold [189] reports a case of extraosseous and apparently extrabursal chondroma of the big toe of the left foot. The patient was a man 42 years of age. Excision of the tumor was performed without wide resection, and no recurrence had taken place within a year. The author suggests that these tumors can be considered benign with reasonable certainty. Stabler [190] reports 2 cases of enchondroma. In 1 the tumor was asymptomatic and operation was not performed. In the other the tumor was curetted and was found to be a chondroma. He emphasizes that operation is not necessary if one is certain of the diagnosis.

[ED. NOTE.—Chondromatous tumors tend to recur unless thoroughly removed. Microscopically, they are often benign, but grossly they react as locally malignant lesions; that is, they recur and may attain such size that they are inoperable.]

Giant Cell Tumors.—Benign Giant Cell Tumors: Garber [191] classifies cystic disease of bone as follows: (1) solitary bone cyst; (2) acute polycystic bone cyst; (3) multiple osteitis fibrosa cystica (von Recklinghausen) and (4) benign giant cell tumor. He emphasizes that this is a disease of adults which usually appears in the epiphyses and is usually preceded by trauma and by pain and swelling. As a rule, no periosteal reaction is seen on roentgenologic study. The gross lesion generally is hemorrhagic and friable. Microscopic examination reveals fibrous proliferation and formation of new bone. Giant cells with 15 to 200 nuclei and stromal round cells and spindle cells are present. Changes in blood supply to bone following trauma and resultant upset in the osteoclastic activity were emphasized

188. Jaffe, H. L., and Lichtenstein, L.: Benign Chondroblastoma of Bone: A Reinterpretation of the So-Called Calcifying or Chondromatous Giant Cell Tumor, Am. J. Path. **18**:969-991 (Nov.) 1942.

189. Gold, A. M.: Extra-Osseous Chondroma of the Foot: Case Report, Bull. Hosp. Joint Dis. **3**:134-140 (Oct.) 1942.

190. Stabler, F.: Degenerate Enchondroma of the Femur and Tibia, Brit. J. Radiol. **15**: 269-271 (Sept.) 1942.

191. Garber, J. N.: Giant Cell Tumors of Bone, Quart. Bull., Indiana Univ. M. Center **4**:10-14 (Jan.) 1942.

as etiologic factors. There is a tendency for recurrence after apparent eradication. The authors feels that the best form of treatment is curettage and cauterization and filling of the cavity with bone chips.

A Cabot case [192] is reported in which the patient, a man 35 years of age, had had disability of the right elbow for one month. He had received a blow on the elbow one year previously and had had occasional pain in the elbow since. There was limitation of extension of a few degrees. Roentgenograms revealed a multilocular cystic area in the medial epicondyle of the humerus. At operation, the cavity was found to contain yellowish and pinkish friable material. Curettage was performed and the cavity allowed to remain empty. Microscopic examination revealed a benign giant cell tumor. The patient was observed for two and a half years and received three courses of roentgen therapy. There was some question of enlargement recurring, and the flexion deformity increased. The tumor was removed, and arthrodesis of the ulnohumeral joint was performed. The patient was a laborer and needed a stable, painless joint.

Kaplan [193] reports a case of giant cell tumor of the vertebra with hemorrhage into the neoplasm and resulting acute compression of the spinal cord. The patient was a woman 22 years of age. Recovery followed excision of the tumor. He also reports a case of hemangioendothelioma of the vertebra with hemorrhage into the tumor and acute compression of the spinal cord. The patient was a woman 44 years of age. Recovery followed excision of the tumor. He stresses the importance of early recognition of the acute compression of the spinal cord and its immediate surgical relief.

Malignant Giant Cell Sarcoma: "Atypical giant cell tumor" is interestingly described by Coley and Miller [194]:

> The typical giant cell tumor is well recognized as a lesion which, while benign, is locally invasive and may recur after treatment. Its most frequent site is the epiphyseometaphyseal regions, with extension in advanced cases into the adjacent diaphysis. Save for rare exceptions, the lesion is subcortical in origin and tends to destroy the cancellous cortical bone. As it progresses, the cortex is reduced to a thin shell or may disappear entirely, although the periosteum remains as a limiting membrane offering resistance to extension into the overlying soft parts.
>
> Distinctly atypical cases are rarely encountered. However, the importance of recognizing them is obvious, for unless their nature is appreciated, the proper treatment cannot be carried out.
>
> The atypical cases may be divided into two groups: (1) atypical because of clinical and pathologic criteria, and (2) atypical because of location.
>
> In the first group are those giant cell tumors that are malignant at the time of first observation, the diagnosis being based on study of tissue removed prior to the administration of any form of treatment; and also those tumors that are believed to have undergone a malignant transformation following unsuccessful treatment, i. e., curettage, irradiation, or both.
>
> In the second group is found that rare example of an expanding osteolytic lesion involving the shaft of a long bone rather than the extremity. The roentgenographic appearance does not simulate that of a malignant tumor, although, from its location, a benign giant cell tumor is not suspected. Under conservative surgery or irradiation this lesion responds in the manner of a giant cell tumor, and sections of tissue are so diagnosed by the pathologist, although, in some instances, a report of "angioma of bone" may be returned. In these cases, there may be reactive hyperplasia with fibrosis and giant cell areas.

192. Giant Cell Tumor of Humerus, Cabot Case 28141, New England J. Med. **226**: 571 (April 2) 1942.

193. Kaplan, A.: Acute Spinal Cord Compression Following Hemorrhage Within Extradural Neoplasm: Report of Two Cases with Recovery, Am. J. Surg. **57**:450-456 (Sept.) 1942.

194. Coley, B. L., and Miller, L. E.: Atypical Giant Cell Tumor, Am. J. Roentgenol. **47**:541-548 (April) 1942.

As to the importance of these atypical giant cell tumors, it is obvious that those that are malignant from the outset should be recognized and treated as malignant tumors. This implies the use of radical surgery with or without preliminary irradiation.

In the more frequently observed examples of malignant transformation of a benign tumor, the factors that have led to such alteration of growth deserve a careful consideration. It must be acknowledged that a completely satisfactory explanation of the cause or causes of this alteration has never been offered. In collaboration with Stewart and Farrow the records of the Memorial Hospital and the Hospital for Ruptured and Crippled were reviewed and found to contain 7 unquestionable examples of such malignant transformation of a previously benign giant cell tumor.

Where the tumor occupies an atypical location, it is essential that its benign nature be recognized so that conservative treatment can be employed. In one such case personally observed, a recurrence took place after biopsy and incomplete removal; irradiation, however, yielded an excellent result. It seems not unlikely that, in the past, amputation may have been performed for such tumors under the mistaken impression that the lesion was an osteogenic sarcoma of osteolytic origin.

The following quotation has been taken from an article on primary malignant giant cell sarcoma of long bones by Meyerding and Broders [195]:

We wish to report a series of seven cases of tumor of the long bones in which the lesion was recognized as malignant at the time of operation and which, following recent microscopic study, we have classified as primary malignant giant-cell sarcoma. While there may be objections to the use of the term, "primary malignant giant-cell sarcoma," we have used it here in the sense that the giant-cell tumor was malignant at the time of the first microscopic examination. This group of tumors does not include those benign foreign body giant-cell tumors which were recognized originally as benign and which subsequently underwent a malignant transformation. Furthermore, we recognize a rare osteogenic type of sarcoma which may contain numerous foreign body giant cells that mask its true malignant nature.

The lesions in the seven cases herein reported are giant-cell tumors which apparently show primary malignant changes in the stroma and are here designated "primary malignant giant-cell sarcomas." In six cases the lesion occurred in both epiphyses and the lower part of the femur and in one case in the upper epiphysis and the upper part of the diaphysis of the tibia; all, therefore, occurred at the knee joint. In no case did we encounter malignant giant cells as the malignancy was always found in the tissue between the foreign body giant cells. Three of these patients have died, one within three months, one within five months, and one three years and seven months after treatment; one of these three had biopsy and irradiation and two had amputation and irradiation. The remaining four patients are still living, one four years, one ten years, one twelve years and one fifteen years after treatment; all of these four patients had amputation and irradiation.

Amputation following early diagnosis and pathologic proof of malignancy is the treatment of choice in cases of this type.

Vascular Tumors.—Thomas [196] reports the results of a pathologic and clinical study of 27 cases of vascular tumor of bone from the Registry of Bone Sarcoma. There are several reasons why there has been confusion regarding vascular tumors. Histologists and pathologists have not agreed as to what should be called endothelium. The reason for this is that in the adult form it is often impossible to distinguish squamous areas of mesenchymal cells (endothelium) from those of ectodermal or entodermal origin. Adult cells similar in structure and arrangement may have a totally different embryonic origin and quite different developmental potentialities. For this reason attempts to identify and classify neoplasms of the so-called endothelial group have proved difficult and controversial. A simple and workable classification is one which considers vascular tumors as endotheliomas accompanied by a very definite vasoformative tendency with endothelial proliferation and formation of new blood vessels. The tumors may be classified as (1) benign

195. Meyerding, H. W, and Broders, A. C.: Primary Malignant Giant-Cell Sarcoma of Long Bones, Tr. West. S. A. (1941) **51**:76-95, 1942.

196. Thomas, A.: Vascular Tumors of Bone: A Pathologic and Clinical Study of Twenty-Seven Cases, Surg., Gynec. & Obst. **74**:777-795 (April) 1942.

angioma, a slowly growing, highly differentiated tumor, congenital in origin, with definite well formed blood vessels and an innate tendency to regress and heal, and (2) malignant angioma, a more cellular and compact growth, with active endothelial proliferation and invasiveness, which shows a tendency to revert to its primitive mesenchymal structure. In certain cases of malignant angioma it is possible to identify two subdivisions, namely angioendothelioma and angiosarcoma. The angioendothelioma shows a rather marked cellular proliferation, and as it has a tendency to revert to a primitive mesenchymal structure the cells assume a cuboidal appearance and alveolar arrangement closely resembling those of epithelial tissue. Nevertheless formation of new blood vessels is evident. In angiosarcoma the vasoformative tendency is much more prominent. This formation of new vessels is the predominant feature of the tumor and enables it to be more easily identified as a true vascular tumor.

In the 12 cases of benign angioma 6 of the patients were males and 6 were females. The ages of the patients ranged from 15 to 62 years. The vertebrae probably formed the most common site of involvement. The treatment consisted of irradiation or operation or both. The author quotes Meyerding as stating that he found angioma of bone to be somewhat radiosensitive and that the use of moderate doses repeated at regular intervals for a number of months caused it to regress gradually and to heal.

In the 15 cases of malignant angioma 8 of the patients were males and 7 were females. The ages of the patients ranged from 3 to 53 years. In the majority of cases the tumor occurred during the second and third decades of life. The long bones were the ones most frequently involved. Multiplicity of the lesion was found in 6 cases. Amputation was performed in 9 cases, with apparent cure in 4. In 1 case the operation had been performed recently. Exploration and curettement were performed in 1 case, and there was no recurrence in more than ten years. Irradiation was employed in 10 cases; death occurred in 6 of these. The 4 surviving patients were treated by irradiation and amputation.

[ED. NOTE.—This is an interesting and informative article written on this rather rare condition and supplies a very good résumé of the literature on the subject.]

Ackermann and Hart [197] report a case of primary hemangioma of the bones of the extremity and state that a survey of the literature revealed it to be the sixteenth such case on record. Their patient was a white boy 15 years of age, whose chief complaint was progressive, painless swelling of the left ankle and knee of four years' duration. Eighteen months prior to his admission he had injured his ankle and had used crutches. Examination revealed a uniform enlargement of the ankle and a fusiform swelling of the left leg just below the knee, which were not tender. Roentgenographic examination revealed multiple hemangioma of the proximal and distal ends of the shaft of the tibia and proximal end of the shaft of the fibula. Microscopic examination of the specimen removed from the distal end of the shaft of the tibia revealed hemangioma. In 1940, or ten years after the patient's first examination, the roentgenogram also showed involvement of the bones of the foot. The gross pathologic examination showed that no bone was exempt. There were gross uniform expansion of bone and multiple cystic cavities of various size which were filled with bloody fluid. Microscopic examination revealed the usual cavernous type of hemangioma with large irregular endothelium-lined spaces filled with erythrocytes. The cavernous spaces were separated by compact fibrous tissue. Roentgenographic examination revealed fusiform enlargement of the epiphysial ends of the bones or of the segments close to the nutrient artery. The tumor was

197. Ackermann, A. J., and Hart, M. S.: Multiple Primary Hemangioma of the Bones of the Extremity, Am. J. Roentgenol. **48**:47-52 (July) 1942.

central in origin; as it enlarged, it caused the bone to expand. The medullary border of the cortex was usually irregular. The bone trabeculae within the tumor were coarse and denser than the normal cancellous bone. The involved bone was often loculated. The periosteum remained intact. The tumor did not involve the epiphysial cartilage and had not penetrated into the joints. The treatment of choice is irradiation.

Kleinberg [198] reports a case in which angioma involved the cuboid bone, the external cuneiform bones and the soft tissue of the foot. The patient was a girl 19 years of age. She had had intermittent limp for eleven years and had had occasional pain and disability. There was a tender mass on the plantar surface of the foot. Excision of the tumor and the subsequent use of roentgen therapy produced a good result.

Malignant Hemangioendothelioma: Aitken [199] presents a concise and thorough summary of the confused state existing regarding Ewing's sarcoma, clinically as well as histologically. He expresses the opinion that it is a rarity and that there is lack of uniformity as to the constitution of the lesion. He says that the diagnosis never can be accepted until there is gross, histologic and postmortem proof of the true nature of the lesion, since clinically it can be simulated by numerous other malignant as well as benign lesions. The author reports a case in which the clinical features and biopsy indicated Ewing's sarcoma of bone, whereas necropsy revealed a primary adrenal neuroblastoma and metastatic involvement of bone. The patient was a girl 16 years of age. She had had intermittent pain in the lower part of the leg for six months, but there was no history of trauma. The temperature and pulse rate were normal. There was slight swelling at the middle third of the right tibia, which was hot and slightly red. Nothing else of significance was found. Roentgenograms of the tibia revealed a diffuse osteoplastic process with some subperiosteal formation of bone of parallel type. Roentgenologic examination of the thorax did not disclose any abnormality.

Local roentgen irradiation was instituted after biopsy, and although 3,264 r was given, subsequent roentgenographic study of the tibia showed no change in the bone. Later, because of drowsiness, irritability and vomiting, a roentgenologic study of the skull was made. The appearance was similar to that seen in cases of increased intracranial pressure. Craniotomy disclosed an extradural mass, which was a highly cellular malignant tumor. Irradiation was applied again to the right tibia and to the skull. A second roentgenographic study showed no significant changes in the bone after this course of treatment. The patient's condition became progressively worse, and death occurred.

Necropsy revealed an ill defined retroperitoneal tumor, metastatic involvement of the mandible, early deposits in the shafts of both humeri and some secondary deposits in both the lungs and the pleura and in the lymph nodes of the thorax. Generally, all signs, symptoms and laboratory findings were commensurate with a diagnosis of Ewing's tumor up to the time of the necropsy.

[Ed. Note.—In many publications one of the editors (H. W. M.) has emphasized that the true nature of this lesion may not be determined until pulmonary metastasis occurs, or until necropsy.]

Heiligman [200] reports a case of sarcoma of the femur in which the patient was a white boy 19 years of age. Death occurred in twelve months as a result of

198. Kleinberg, S.: Angioma of Foot, J. Bone & Joint Surg. **24**:367-371 (April) 1942.

199. Aitken, S. G.: Metastatic Neuroblastoma in Bone, New Zealand M. J. **41**:209-212 (Oct.) 1942.

200. Heiligman, R.: Atypical Ewing Tumor: Problem in Diagnosis, Bull. Hosp. Joint Dis. **3**:41-46 (Jan.) 1942.

multiple metastatic involvement. Disarticulation at the hip was performed after a needle biopsy and subsequent incision biopsy. The pathologic report was of malignant tumor. Necropsy revealed that metastasis had occurred and involved the spinal cord, the ribs, the sternum, the pelvis and the skull. The intermittent symptoms and history pointed to Ewing's sarcoma.

Barden, Belk, Pratt and Taylor [201] report a case in which the patient was a boy aged 5 years. He was seen in February 1940. There was a history of intermittent pain and fever. Pain was situated in the lower part of the right leg and knee, and swelling and tenderness were present. The symptoms were migratory and simulated those of acute articular rheumatism (other points of involvement were the knees, ankles and elbows). Tenderness along the shafts of the adjacent long bones was noted, and cardiac symptoms were present. Roentgenographic examination revealed punched-out areas in the skull, the pelvis and the diaphyses of the femurs and tibias and typical proliferation along the shafts of the long bones. Supportive therapy and roentgen therapy for relief of pain in the bones and joints were instituted. The patient failed gradually and died about eight months after his admission to the hospital and fifteen months after onset of symptoms. Biopsy revealed a collection of large, pale cells with densely chromatic nuclei. The cells were arranged in pavement fashion and corresponded to the cells of Ewing's sarcoma (endothelial myeloma).

Sloat and Peterson [202] report a case of Ewing's tumor of the sacrum in which the patient was well five years after the diagnosis was made by biopsy. Intensive roentgen therapy was employed. This consisted of courses of 7,000 r, 4,611 r and 2,522 r.

Adamantinoma.—Dockerty and Meyerding [203] report 2 cases of adamantinoma of the tibia and state that extracranial adamantinomas are rare neoplasms that occur in bones (tibia and ulna) in which a sharp ridge of osseous tissue closely approximates the overlying skin. Prior to 1942, 15 cases of this tumor had been reported.

In the first case reported by these authors the patient was a pregnant woman 24 years of age, who complained of intermittent pain of eight years' duration and a "lump" which had been present on the left shin for fifteen months. Roentgenograms had been interpreted as indicating an atypical giant cell tumor, and biopsy had suggested a metastatic malignant process. Amputation was performed for a large adamantinoma.

[Ed. Note.—One year later metastasis appeared in the inguinal lymph nodes, and death occurred shortly thereafter.]

In the second case the patient was a man 27 years of age, who had noticed the tumor following a "shearing" type of trauma of the left tibia which had occurred at the age of 10 years. One pathologic fracture had occurred. After several operations the growth apparently was successfully removed.

The site of the lesions combined with the frequent history of injury suggests that local trauma may play some part in the production of tibial adamantinoma. The tumor is of slow evolution but is so invasive that amputation of the leg almost always becomes necessary. Metastasis is possible. Roentgenologically, the appearance suggests a giant cell tumor, but invasion of soft parts indicates atypical (malignant) characteristics. Microscopically, the lesion is liable to be mistaken for

201. Barden, R. P.; Belk, W. P.; Pratt, G. E., and Taylor, W. R.: Ewing's Endothelial Myeloma with Extensive Skeletal Involvement, Radiology **39**:334-336 (Sept.) 1942.

202. Sloat, J. I., and Peterson, L. T.: Ewing's Tumor of the Sacrum, J. A. M. A. **119**: 1499-1500 (Aug. 29) 1942.

203. Dockerty, M. B., and Meyerding, H. W.: Adamantinoma of the Tibia: Report of Two New Cases, J. A. M. A. **119**:932-937 (July 18) 1942.

metastatic carcinoma. The cellular pattern varies from that of a basal cell or squamous cell carcinoma to an adenocarcinoma. Intermediate histologic pictures in which the cells resemble ameloblasts have been responsible for the use of the term "adamantinoma." The authors concur in the belief that tibial adamantinomas arise from the basal layers of the overlying skin and that the bone "tumor" accordingly represents secondary invasion. In 1 of their cases there was evidence of such a primary cutaneous malignant process.

Bell [204] reports a case of adamantinoma of the femur and mentions the comparative frequency of this lesion in the jaws. His case is the first one of adamantinoma of the femur that has been reported. The patient was a native African 16 years of age. He complained of pain in the left knee, aggravated by motion, and of a swelling of the lower end of the femur. The temperature ranged from 98 to 100 F. A diagnosis of deep abscess was made. An exploratory incision did not disclose any pus; instead, there was a fleshy growth, which was incised. The femur contained bony spicules and irregular masses. The patient died five weeks later. Microscopic examination revealed cellular strands in a vascular fibrous stroma. The cells were spindle shaped or stellate, with a surrounding layer of high columnar epithelium.

Anderson and Saunders [205] report a case of adamantinoma of the ulna in which the patient was a man 49 years of age, who had sustained fractures of the right arm above the wrist in 1902 and 1905. In 1929 there was a palpable dislocation of the head of the radius with limitation of supination and diffuse swelling over the ulnar side of the forearm. Roentgenographic examination revealed a rarefying process which extended to within an inch (2.5 cm.) of either end of the ulna. The distal part of the cortex was thin and contained large round and smaller foamlike lobules; the remainder of the involved region had a more dense appearance with honeycombed trabeculae. The lower portion of the shaft of the ulna was resected and a tibial graft inserted. Good recovery occurred, and the patient was free of symptoms for four years. Weakness and paresthesia of the right arm then recurred. Roentgenographic examination at this time showed that the disease had involved the ulna and the bone graft. Temporary relief of pain followed the use of roentgen therapy. The values for calcium, phosphorus and phosphatase in the serum were normal. One month later roentgenographic examination showed complete absence of bony cortex over the tumor and extension of the tumor into the soft tissues. An attempt was made to resect the ulna and the tumor, but this was impossible and part of the tumor remained. Pain recurred two months later, and amputation was performed through the lower portion of the humerus. The patient had remained in excellent health without evidence of recurrence or metastasis for six years.

The tumor was an infiltrating epithelial type of lesion. It originated from the basal cells that grew in fibrous tissue stroma. It had, to a certain extent, the histologic characteristics of a tooth bud.

Fischer, in 1913, expressed the opinion that this type of tumor arises from cell rests. Ryrie, in 1932, said that such tumors arise from basal cells implanted in the deeper structures by trauma, and Anderson and Saunders agree with this opinion.

The tumor is a soft, spongy, gray, indistinctly lobulated vascular growth which occupies the central portion of the shaft of the bone and expands it without breaking through the cortex. Microscopically, it is an infiltrating epithelial tumor in a stroma of fibrous tissue.

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204. Bell, A. L.: A Case of Adamantinoma of the Femur, Brit. J. Surg. **30**:81-82 (July) 1942.

205. Anderson, C. E., and Saunders, J. B. de C. M.: Primary Adamantinoma of the Ulna, Surg., Gynec. & Obst. **75**:351-356 (Sept.) 1942.

The tumor is of a low grade of malignancy and does not metastasize. It affects both sexes, and the ages of the patients range from 22 to 46 years. In Bell's case [204] the tumor occurred in an African boy who was 16 years of age. In all the cases reported in the literature there was a history of trauma which was not as severe as a fracture. The first symptom usually is a mass.

Roentgenographic examination reveals a polycystic, expanding central tumor with a sharp outline and a fine trabecular pattern. There is no periosteal reaction. The tumor may be finely honeycombed.

Treatment consists of complete excision of the tumor, resection of the involved bone or amputation of the affected limb. Radiosensitivity of the tumor is low, and there is a tendency for it to recur if it is not completely removed.

Tumors of the Spinal Canal.—French and Peyton [206] report 3 cases of proved mixed tumor (teratoma) of the spinal canal. In all 3 cases there was a characteristic history of symptoms of long duration before the patient became incapacitated, and there was roentgenologic evidence of fusiform enlargement of the spinal canal and of spina bifida. When the interpedicular distance of a spinal canal is larger than normal (or an increase of 2 to 4 mm. is present in consecutive vertebrae), this evidence is consistent with a diagnosis of mixed tumor. The authors have noted that a similar chronicity of symptoms and similar roentgenologic changes are present in cases of lipoma. They say that roentgenologic examination produces evidence of fusiform pressure erosion over several vertebrae. The first sign is thinning of the lamina and narrowing of the pedicles, with a resulting increase in the distances between the pedicles; later, there is erosion of the posterior surfaces of the bodies of the vertebrae.

In discussing tumors simulating protrusion of an intervertebral disk, Nosik [207] reports 3 cases of pain low in the back with sciatica in which there was a textbook picture of protrusion of an intervertebral disk. Laminectomy revealed melanoma, neurofibroma and plasma cell myeloma. He stressed the fact that at this time, when protruded disk has been brought to the front in diagnosis, it is easy to overlook the fact that other, rarer lesions can and do produce symptoms identical with those of protrusion of an intervertebral disk.

Conley and Miller [208] report a case of neurilemmoma of the first sacral vertebra in which the patient was a woman 32 years of age. The symptoms consisted of pain along the left sciatic nerve, which began in 1928. The patient was seen in 1939, at which time examination revealed atrophy of the left thigh and calf, a limp and a steppage gait. There were definite reflex and sensory changes in the left leg. Roentgenographic examination revealed rarefaction of the left side of the body of the first sacral vertebra. Operation consisted of exposure and curettage of the cystlike cavity. Roentgen therapy was given weekly for ten weeks, and the patient remained under observation for three years. Serial roentgenograms revealed bony replacement in the cavity. The pain was relieved, and sensation returned. The original atrophy remained. The tumor consisted of palisaded nuclei and loose connective tissue stroma.

Siris and Angrist [209] report a case of chondroblastic meningioma in which the patient was a boy 18 years of age. This is the twenty-sixth case of this type

206. French, L. A., and Peyton, W. T.: Mixed Tumors of the Spinal Canal, Arch. Neurol. & Psychiat. **47**:737-751 (May) 1942.

207. Nosik, W. A.: Unusual Tumors Simulating Protrusion of the Intervertebral Disc, Cleveland Clin. Quart. **9**:54-59 (Jan.) 1942.

208. Conley, A. H., and Miller, D. S.: Neurilemmoma of Bone, J. Bone & Joint Surg. **24**:684-689 (July) 1942.

209. Siris, J. H., and Angrist, A.: Chondroblastic Meningiomas, Am. J. Surg. **57**:162-167 (July) 1942.

reported in the literature, and the sixth one in which all of the tumor was removed successfully. There is much speculation as to the site of origin of this tumor. The authors suggest that it possibly may originate from cartilaginous rests misplaced during development of the skull. Transition of meningeal fibroblasts to cartilage cells was mentioned. Another theory is that it may originate from cell rests in the arachnoidal granulations. There are no pathognomonic symptoms or signs. The prognosis is relatively favorable if the tumor is completely excised.

Experimental Work on Diagnosis of Tumors of Bone.—Inclan [210] has used arteriography to diagnose malignant tumors of bone and also has carried out experiments by using different kinds of opaque substances. He expresses the opinion that this method affords an earlier diagnosis of tumors of bone. If the tumor is still limited to bone and if no invasion of soft tissue is yet evident, surgical block excision may be adequate, and in those cases in which amputation is refused this procedure at least offers a possibility of doing something for the patient. The most striking characteristic arteriographic sign of malignant disease of bone is the filling in of the stroma of the new growth by numerous vessels, showing extension of the invading tumor. A second evidence is the presence of new, atypical arterial circulation with pedicles from the main artery and numerous irregular branches entering the bone lesion. Inclan enumerates the objections to this method of diagnosing tumors of bone, but none of them, he says, are sufficient to condemn a procedure which makes possible a positive and early diagnosis of malignant tumors of bone. In addition to the methods previously described for this procedure, he advocates a new technic, which consists of ascending instillation of the opaque substance. He expresses the opinion that this technic will be of value in those cases in which descending arteriography would be either impractical or impossible. He says that the procedure deserves further trial, especially in institutions devoted to the study of cancer, where the real value of the procedure may be ascertained.

Treadwell, Low-Beer, Friedell and Lawrence [211] in their report on "Metabolic Studies on Neoplasm of Bone with the Aid of Radioactive Strontium" state that, experimentally, calcium and strontium have a selective localization in bone. The application of the radioactive isotopes of these substances to clinical metabolic studies and possibly to therapeutic irradiation of bone seemed feasible. The value for serum phosphatase was lowered in those cases of carcinoma of the prostate in which the lesion had metastasized to bone. In 6 cases of tumor of bone they have given radioactive strontium prior to biopsy or amputation, and by postoperative studies of the specimen they have found that the strontium had been taken up chiefly by growing bone and by osteogenic tumor tissue. They express the opinion that various considerations seem to justify the therapeutic use of radioactive strontium in certain cases of tumor of bone.

Treatment of Tumors of Bone.—Copeland [212] says that a bitter lesson has been learned in radiotherapy of tumors of bone, namely, that radiosensitivity does not parallel radiocurability. He says that osteochondroma that occurs singly is curable by surgical excision. He has observed malignant change in a few cases in which multiple osteochondromas were present. Roentgen rays and radium play a slight role in the treatment of this type of tumor.

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210. Inclan, A.: The Possibilities of Roentgenographic Study of the Arterial Circulation in the Early Diagnosis of Bone Malignancy, J. Bone & Joint Surg. **24**:259-269 (April) 1942.

211. Treadwell, A. de G.; Low-Beer, B. V. A.; Friedell, H. L., and Lawrence, J. H.: Metabolic Studies on Neoplasm of Bone with the Aid of Radioactive Strontium, Am. J. M. Sc. **204**:521-530 (Oct.) 1942.

212. Copeland, M. M.: Bone Tumors with Reference to Their Treatment, Surgery **11**: 436-455 (March) 1942.

In cases of chondroma, Copeland says that the site of the tumor is of importance. When the small bones of the hand or foot are involved, the lesion usually is benign, and curettage and excision are advisable. When the tumor involves the sternum, the spinal column, or the long bones, the lesion must be considered as potentially malignant. Surgical treatment and roentgen therapy are advisable in the treatment of this type of tumor, as it is radioresistant.

He feels that primary chondromyxosarcoma usually affects patients who are 14 to 21 years of age. He says that it commonly is situated about the knee, shoulder and pelvic girdle. A subperiosteal shadow streaked with calcium spicules is visible in the roentgenogram. Permanent cure was obtained in 9 per cent of his series of cases. Irradiation relieved pain but was not curative. Amputation was performed in 3 of 5 cases.

Chondrosarcoma may occur as a secondary lesion in cases in which the patients have had chondroma, osteochondroma, osteitis deformans (Paget's disease) or hereditary chondrodysplasia. The bones most frequently involved are the ribs, the femur, the heel bone and the humerus. Roentgenographically the tumor appears as a fuzzy periosteal shadow flecked with calcium. A pathologic fracture may occur. In 18, or 26 per cent, of the cases of chondrosarcoma the patients were living five or more years after operation. Amputation of the affected limb was performed in 8 of these cases; in the remaining 10 a combination of roentgen therapy and surgical treatment was employed.

Copeland expresses the opinion that osteoblastic osteogenic sarcoma usually affects persons between 15 and 25 years of age. He says that the lesion usually is situated in the lower portion of the femur or in the upper part of the tibia. The roentgenographic appearance consists of dense radiating ("sun-ray") shadows and evidence of new bone in the periosteal zone. Later in the course of the disease the medullary cavity is obliterated. In 26 per cent of his cases the patients obtained a cure after amputation or irradiation or a combination of the two.

There has been a trend toward increased conservatism in the treatment of benign giant cell tumor. Copeland says that curettage and cauterization are indicated when the lesion has not reached an advanced stage and that resection and irradiation may be employed in selected cases in which the lesion is advanced. He feels, however, that patients with certain lesions treated by irradiation alone, or by surgical excision alone, obtain a cure, but that unfortunate results may accrue from such a combination. Irradiation employed preoperatively or postoperatively is of little value in the treatment of this lesion.

Chondroblastic sarcoma is a rare osteolytic variant of osteogenic sarcoma. Copeland says that this tumor is most effectively treated by large doses of roentgen rays or radium. Osteolytic osteogenic sarcoma, as shown in roentgenograms, causes bone cells to melt away; it is eccentrically situated. It is not radiosensitive and does not respond to therapeutic doses of roentgen rays or radium. Amputation produced a five year survival rate of 10 per cent in Copeland's series of cases.

Hemangioendothelioma (Ewing's sarcoma or tumor) may be therapeutically tested by irradiation, which also produces the best palliative result. Copeland says that the best five year survival rate can be obtained with preoperative irradiation and radical excision or amputation. Multiple myeloma may be treated palliatively by means of irradiation with roentgen rays or radium, which relieves pain and produces temporary symptomatic improvement.

Fibrosarcoma may be of periosteal or neurogenic origin. The first type has a low grade of malignancy and is highly radiosensitive. Amputation or radical resection results in a cure in the majority of instances. However, the undifferentiated,

oat-cell type of fibrosarcoma does not respond to conservative treatment, and primary amputation is the treatment of choice. Clinical cure of neurogenic sarcoma may be obtained by surgical intervention. Amputation gives the best result, but a permanent cure seldom is obtained.

Angioma of bone is rare and essentially benign. Radiosensitiveness of this tumor varies. Myositis ossificans may be best treated by conservative methods, but therapeutic doses of roentgen rays may be of value in a few cases. The lesions of Hand-Schüller-Christian disease are radiosensitive, and transfusion frequently is indicated.

Higinbotham and Coley [213] in their discussion of osteogenic sarcoma state that the five year survival rate is as follows: 8.5 per cent in cases in which only irradiation is used, 31 per cent in cases in which operation is employed and 34 per cent in cases in which both types of treatment are employed. As a result of a study of 114 cases of osteogenic sarcoma in the past five years, they advise delivering at least 4,000 r to all parts of the tumor and then performing a radical amputation as soon as the skin is healthy enough. The irradiation of each tumor should be planned individually. Its efficacy varies with the different types of osteogenic sarcoma; satisfactory effects are evidenced by a lowering of the value for the serum phosphatase if it was elevated previously. Pain is partially or entirely alleviated. They emphasize that the condition of the skin must be carefully watched. Postamputation irradiation is seldom if ever indicated.

Valls [214] in an article entitled "Osteogenic Sarcoma (Malignant Osteoblastoma, Brachetto-Brian)" exhaustively reviews the literature and submits the term "malignant osteoblastoma" for use in classifying malignant tumors of bone which arise from cells of the osteoblastic or potential bone-forming type but which do not necessarily form bone in the mass. He stresses the inability of roentgenographic examination or of clinical study alone to reveal the type of bone tumor and the need of cooperation of all branches of science in diagnosis and treatment. He considers surgical intervention of prime importance in treatment and roentgen therapy as an adjunct.

Hansen [215] reports a case in which a diagnosis of osteitis deformans had been made when the patient, a man 52 years of age, had fractured his right humerus. After he had worn a cast for six weeks, swelling and burning were noticed and roentgenologic examination revealed destruction of bone. A diagnosis of sarcoma was made. Amputation was at first refused; therefore roentgen therapy was employed. Later, amputation was done for relief of pain. The patient died soon after the operation, and permission for necropsy was not obtained.

Atsatt [216] reports a case of osteogenic sarcoma in which the patient, a cowboy 29 years of age, first reported for examination eleven months after an accident. Five months later, a section of the fibula was removed. Six months later, the recurrent tumor attained considerable size and amputation was performed at the middle of the thigh. Kirkman [217] reports an instance of this type of lesion in

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216. Atsatt, R. F.: Osteogenic Sarcoma as Concomitant of Industrial Accident, Am. J. Surg. **57**:143-146 (July) 1942.

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the humerus. The tumor occurred after open reduction and the use of a beef bone dowel pin; no union was secured at the site of the fracture. Amputation was performed eleven months after the first operation. Atsatt mentioned reports of cases in which sarcoma occurred after open reduction of fractures.

Pack and Braund [218] reviewed the literature on myositis ossificans and found 5 cases in which a malignant neoplastic change of the bony tissue had occurred as a complication of this disease. In 4 of these 5 cases an osteogenic sarcoma occurred as a complication of myositis ossificans traumatica, and in 1 case a sarcoma occurred in a calcified hematoma. They report 3 cases of this complication. In 2 of these cases the sarcoma occurred in preexisting myositis ossificans conscripta, and in the remaining case myositis ossificans progressiva was associated with a malignant tumor, probably a myxoliposarcoma.

Sullivan [219] found reports of about 30 cases of osteosarcoma and chondrosarcoma of the breast, but only 7 or 8 cases of osteochondrosarcoma. He feels that in the majority of cases the exciting agent apparently was trauma. All of the patients were beyond the third decade of life. He reports 1 case in which osteochondrosarcoma followed a severe contusion of the breast.

Geschickter,[220] in an article entitled "Neoplastic and Related Conditions in the Bones of Children," recommends the following simple classification of bone lesions which affect children:

I. Inflammatory
II. Metabolic
III. Neoplastic
  Benign
    Osteochondroma
    Chondroma
    Bone cyst
  Malignant
    Primary—Ewing's sarcoma, osteogenic sarcoma
    Secondary—metastatic

He emphasizes the diagnostic use of roentgen rays in cases of Ewing's sarcoma and says that resection or amputation should be performed after the maximal effect of these rays has been achieved. If resection or amputation is not feasible, subsequent courses of roentgen therapy are given. He says that roentgen therapy alone is never curative in cases of Ewing's sarcoma.

Bassas Grau [221] reports a case of von Recklinghausen's disease in which sarcomatous degeneration occurred as a result of surgical trauma. Caeiro, Zanchi and Bonduel [222] report a case of traumatic sarcoma of the tibial tuberosity.

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218. Pack, G. T., and Braund, R. R.: The Development of Sarcoma in Myositis Ossificans, J. A. M. A. **119**:776-779 (July 4) 1942.

219. Sullivan, S. J.: Osteochondrosarcoma of the Breast, Illinois M. J. **82**:140-141 (Aug.) 1942.

220. Geschickter, C. F.: Neoplastic and Related Conditions in the Bones of Children, Rhode Island M. J. **25**:98-101 (May) 1942.

221. Bassas Grau, E.: Sarcomatous Degeneration in Recklinghausen's Disease, Actas dermo-sif. **33**:368-371 (Jan.) 1942.

222. Caeiro, J. A.; Zanchi, A., and Bonduel, A.: Sarcoma of Traumatic Origin, Rev. Asoc. méd. argent. **56**:153-155 (March 15-30) 1942.

(To Be Concluded)